

**RING-OPENING OF SUBSTITUTED
3-THIENYLLITHIUM DERIVATIVES
AND RELATED SYSTEMS**

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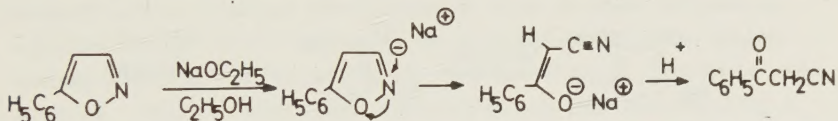
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1. INTRODUCTION

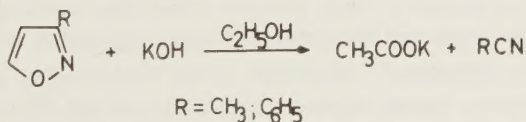
In connection with work on optically active biselenienyls¹ (atropisomerism) in 1969, the author found that 2,5-dimethyl-3-selenienyllithium ring-opened to give 2-hexen-4-yn-2-selenolate, at a temperature as low as -70°C ,² which motivated a more detailed investigation.

1.1 Literature survey

As early as in the 1890's, Claisen and Stock found that 5-phenylisoxazole was cleaved when treated with sodium ethoxide at room temperature.³ The ring-opening was explained as indicated

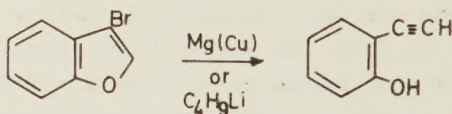


above. An anionic center was created at C-3 and the ring-opening took place formally as an α,β -elimination. In the decade that followed, Claisen investigated the ring-opening reactions of 3- and 5-methylisoxazole, 3- and 5-phenylisoxazole and unsubstituted isoxazole.^{4,5} The 3-substituted derivatives were not so prone to undergo ring-cleavage as the 5-substituted ones, but did so with fragmentation to a nitrile and acetate upon heating with potassium hydroxide in ethanol. The mechanism was, however, not discussed.



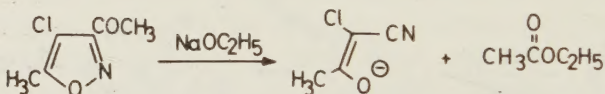
Reichstein et al.⁶ found, about 30 years later, that 3-benzo[b]furylmagnesium bromide was unstable and isolated a 28 % yield of o-hydroxyphenylacetylene. The reaction was not further developed. An analogous reaction took place with 3-benzo[b]furyllithium, which was reported by Gilman and

Melstrom in 1948.⁷ As will be seen later in this thesis, these



results are not in accordance with the behavior of 2,5-dimethyl-3-thienyl- and 2,5-dimethyl-2-selenienylmagnesium iodide compared with the corresponding lithium derivatives.⁸

Quilico et al.⁹ discovered a ring-opening reaction, similar to that of Claisen, when 3-acetyl-4-chloro-5-methylisoxazole was treated with sodium ethoxide (1946). A further kind of ring-



opening was reported in the benzo[b]furan series. Gaertner^{10a} showed that 2-chloromethylbenzo[b]furan produced ortho allenylphenol when treated with magnesium in a special reactor. In this case the ring-opening was suggested to take place from the side chain of the Grignard reagent. It was also shown by the same

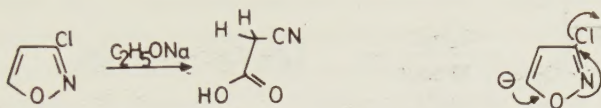


author^{10b} that 3-methyl-2-benzo[b]thenylmagnesium chloride undergoes a similar cleavage, although less willingly.

In 1959 once again a benzo[b]furyllithium derivative was reported to ring-open, namely 2,3-dilithiobenzo[b]furan (Kolb, 1959¹¹).

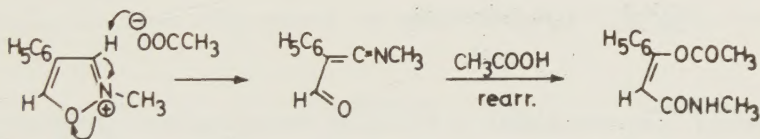


A ring-opening reaction of 3-chloroisoxazole took place when this substance was treated with base (Quilico et al., 1961¹²).



This reaction is superficially analogous to Claisen's ring-opening of 3-substituted isoxazoles.⁴ However, in the above reaction, chlorine acts as a leaving group. In the case of 3-methyl- or 3-phenylisoxazole, no substituent could act as such and instead the $\text{C}_3\text{-C}_4$ bond was broken.⁴

Woodward and Olofson¹³ showed that isoxazolium salts undergo ring-cleavage when treated with as weak a base as acetate ion to give initially an α -ketoketeneimine, which ultimately was converted to an enol ester after reaction with acetate (1961). When the N-methyl group was replaced by a



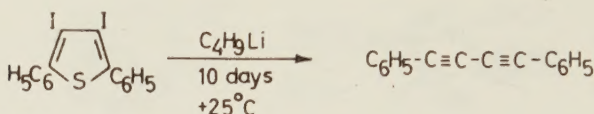
t-butyl group, the α -ketoketeneimines could be isolated when the base was e.g. triethylamine.¹⁴ (Further development of this reaction led to the so-called Woodward peptide synthesis.)

During rearrangement experiments with 3-thienyllithium derivatives Gronowitz and Moses¹⁵ noticed that unsaturated aliphatic compounds were formed when 3-thienyllithium was allowed to stand at room temperature for several hours (1961).

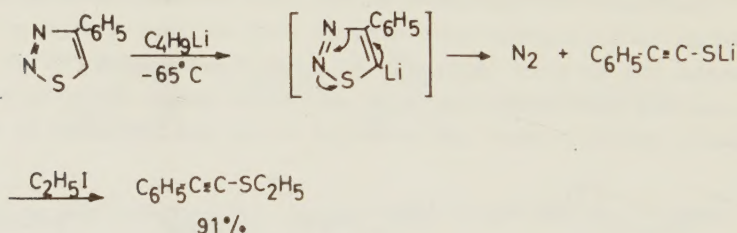
In a paper from 1963, Angeloni¹⁶ reported that 2-phenyl-3-benzo[b]furylmagnesium bromide ring-opened to o-hydroxy-diphenylacetylene, a reaction quite analogous to that of Reichstein et al.⁶

In 1968, several papers concerning base induced ring-opening reactions of heterocycles appeared. Wittig and Rings¹⁷ found in connection with their work on the elusive dehydrothiophene, that 2,5-diphenyl-3,4-diiodothiophene produced 1,4-di-

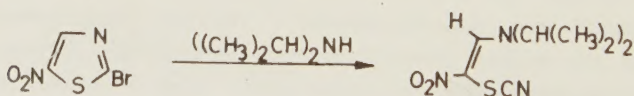
phenyl-1,3-butadiyne after treatment with butyllithium. A



cleavage of 1,2,3-thiadiazoles was noticed by Raap and Micetich.¹⁸ Thus when 4-phenyl-1,2,3-thiadiazole was treated with butyllithium at -65°C , nitrogen and an acetylenic thiolate were formed. The latter was alkylated on sulphur by an alkyl halide. When 2-bromo-5-nitrothiazole was treated with secondary



amines, preferentially sterically demanding ones, enamino-thiocyanates were obtained (Ilvespää¹⁹). It was suggested that

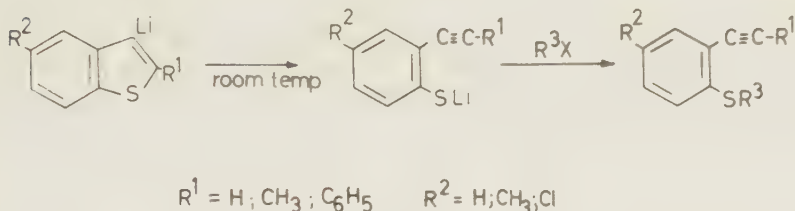


bulky amines, such as diisopropylamine attacked the 4-position rather than the 2-position. The reverse reactivity was the case with sterically less demanding amines such as dimethylamine. The mechanism of the ring-opening was formulated as follows.

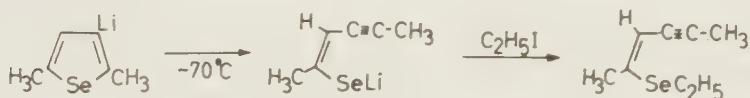


The expulsion of the bromide ion resembles the chloride expulsion in the 3-chloroisoxazole case.¹²

In a paper that also appeared in 1968, Iddon and Dickinson²⁰ mentioned that "rearrangements" occurred leading to a mixture of products, when 3-benzo[b]thienyllithium was prepared at 0°C. However, no evidence of ring-opening was presented at that time. In a series of papers²¹⁻²⁵ (1970-1971), the above authors demonstrated the ring-opening of some 3-benzo[b]thienyllithium derivatives.

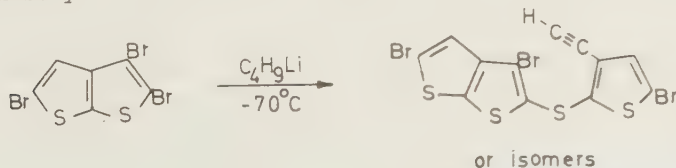


In 1969, Gronowitz and Frejd² found that 2,5-dimethyl-5-selenienyllithium ring-opened rapidly even at -70°C. This obser-

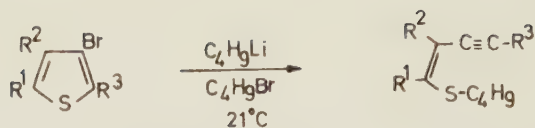


vation started the investigation of ring-opening reactions of some heterocyclic lithium compounds,^{8,26-28} which is the topic of this thesis.

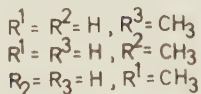
Bugge²⁹ and Jacobsen³⁰ reported in 1969 and 1970 that 2,3,5-tribromothiopheno[2,3-b]thiophene and some 3-bromothiophene derivatives, respectively, yielded acetylenes upon treatment with butyllithium.



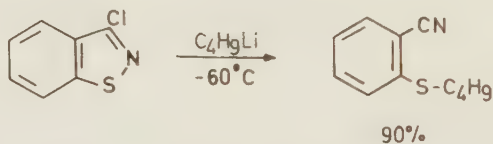
Ref. 29



Ref. 30

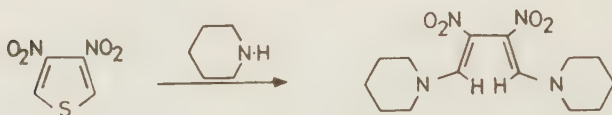


A facile ring-opening was observed by Carrington et al.³¹ (1971) when 3-chloro-1,2-benzisothiazole was treated with various bases. As an example, *o*-(*n*-butylthio)-benzonitrile was formed in high yield when the chlorobenzisothiazole was treated with *n*-butyllithium even at -60°C. Two mechanisms were suggested:

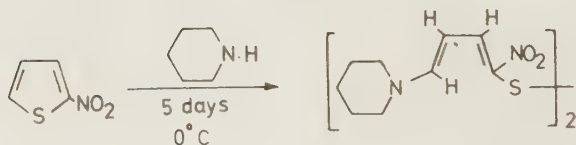


1) attack at the sulphur atom by the *n*-butyl anion resulting in ring-opening or 2) metal-halogen exchange followed by ring-cleavage and subsequent alkylation at sulphur by *n*-butylchloride formed or by *n*-butylbromide from the *n*-butyllithium preparation. The latter mechanism was suggested to be most likely (cf. 2.8.1).

Dell'Erba et al.^{32,33} showed that 3,4-dinitrothiophene and 2-nitrothiophene were cleaved by secondary amines. The mechanisms



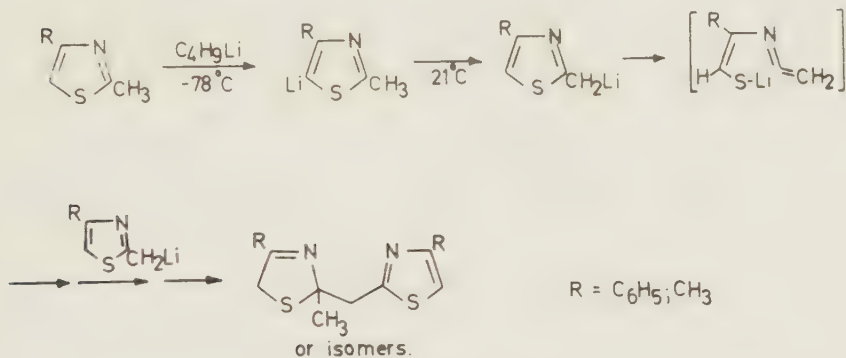
Ref. 32



Ref. 33

of these reactions were not discussed.

When some 4-substituted 2-methyl-5-thiazolylethyl lithium derivatives, prepared at -78°C in tetrahydrofuran, were allowed to reach room temperature, a rearrangement took place leading to 2-lithiomethylthiazoles, which were cleaved to keteneimines (Meyers and Knaus, 1973³⁴). The reaction conditions did not permit the isolation of the keteneimines, since these electrophilic substances attacked the 2-lithiomethylthiazole left in the reaction mixture giving rise to a dimer of the 2-methylthiazole derivative.



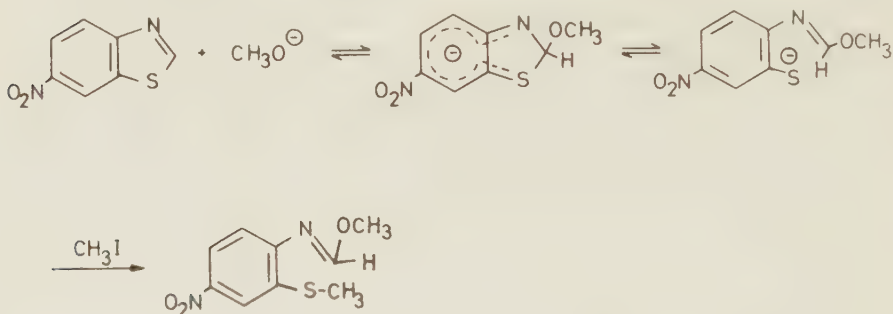
In a recent publication Renson et al.³⁵ described the ring-opening of 2-methyl-3-benzo[b]selenienyllithium to lithium o-(1-propynyl)-phenyl selenolate. In the light of Iddon's and



Dickinson's work,²¹⁻²⁵ this result was expected. However, it was not expected that 3-benzo[b]selenienyllithium should be quite stable at room temperature for several hours, which was demonstrated by Renson et al.³⁵ It was also suggested that 2,3-dilithiobenzo[b]selenophene was responsible for a relatively fast ring cleavage even at -80°C (cf. 2,3-dilithiobenzo[b]furan¹¹). This also contrasted sharply with 2,3-dilithiobenzo[b]thiophene, which was reported by Ried and Bender to be stable

at room temperature.³⁶ Obviously the analogy between different heterocyclic systems can not be drawn too far.

6-Nitrobenzothiazole was also reported to be subject to ring-cleavage (Bartoli et al.³⁷ 1974). Methoxide (in dimethylsulphoxide) was suggested to attack the 2-position, giving rise to a Wheland intermediate in equilibrium with its isomeric fission product. Subsequent alkylation at sulphur with methyl



iodide gave a quantitative yield of 2-methoxymethyleneimino-5-nitrophenylmethylsulphide.

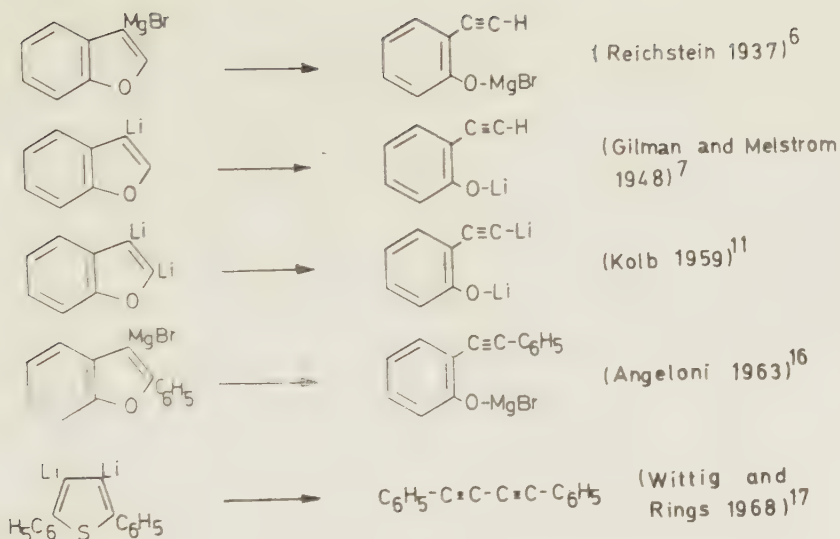
1.2 Discussion of the problem

Evidently there were several ring-opening reactions described in the literature at the beginning of this work (1969), but only five cases seemed to be of interest (see Scheme 1).

These reactions possessed the common feature, that an "aromatic" nucleus was cleaved under certain conditions, when the metal atom was directly attached to the aromatic ring in the so-called β -position. The mechanisms of these ring-opening reactions were little discussed.

In a previous communication, Gilman et al.³⁸ reported that 2,3,5-triphenyl-4-furyllithium was stable enough to give a 78 % yield of the carboxylic acid upon carbonation. However, no temperature was given. 3-Furylsodium was also shown to be sufficiently stable at $+115^\circ\text{C}$ to give a 0.5 % yield of 3-furoic acid.³⁹

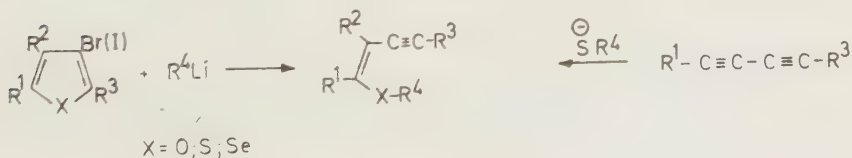
Attempted preparation of 3-selenophene aldehyde⁴⁰, 3-deu-



Scheme 1

terioselenophene⁴¹ and 3-selenophenecarboxylic acid⁴² by using 3-selenienyllithium followed by dimethylformamide, deuterioacetic acid, and solid carbon dioxide, in that order, was reported to give very low yields of the desired substances. It was possible that ring-opening reactions were responsible for these results. (However, see p 29.)

Naturally it was interesting to find out whether the ring-opening reaction was general among the monocyclic heteroaromatic compounds with one heteroatom. If this were the case, a convenient synthesis of the ene-yne backbone might be achieved (Scheme 2). This structural unit is present in some natural



Scheme 2

products isolated and identified by Bohlmann et al.⁴³ from Compositae. Many conjugated polyacetylenic vinylthioethers have also been prepared by Bohlmann and coworkers⁴³ by careful multi-step syntheses, often starting from other polyacetylenic compounds. The synthesis of some thioenynes has been accomplished by Petrov et al.^{44a} and Shostakovskii et al.^{44b} by adding e.g. ethylthiolate across one of the triple bonds in dialkyl-substituted diacetylenic derivatives (Scheme 2). The mode of addition was stereospecifically "trans" in accord with the findings of Truce et al.⁴⁵

It should also be mentioned that the addition of sodium methylmercaptide to carbon-carbon triple bonds of some more complicated acetylenes gave mixtures of cis- and trans-addition, as reported by Bohlman et al.⁴⁶ Obviously there are exceptions to trans-addition when other functions in the molecule may influence the stereochemistry of the reaction.

By using the aromatic nucleus in e.g. thiophene as a matrix for placing substituents in desired positions, it would be possible to obtain otherwise difficultly available conjugated vinylacetylenic thioethers with trans stereochemistry by performing a ring-opening reaction of the heterocyclic β -lithium derivatives in the last step.

On the other hand, it might often be desirable to avoid ring-opening of β -heteroaryllithium derivatives, since these reagents are of great value for preparing substituted heterocycles. It was then considered important to establish the conditions under which ring-opening prevails.

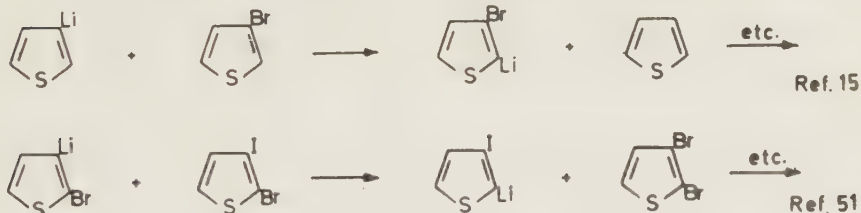
Obviously the influence of different substituents and their positions in the aromatic ring on the ring-opening reaction had to be examined. As a model the thiophene nucleus was chosen, but some experiments in the selenophene and furan series were also considered of interest. Thus, regarding the ring-opening reaction, it should be possible to compare these three ring systems to some extent.

The general way of placing a lithium substituent in the β -position of these heterocycles and their derivatives is by halogen-metal exchange between a β -bromo or β -iodo compound and an alkyl- or aryllithium reagent. Consequently such β -halo heterocycles with suitable substituents in the remaining

positions had to be prepared.

Also worth mentioning is the fact that it is possible to metalate the β -positions selectively in some specially substituted thiophene derivatives. Thus 2,5-dichlorothiophene was metalated by lithium diisopropylamide⁴⁷ and 2-methoxy-5-methylthiophene by *n*-butyllithium.⁴⁸ The latter compound was selectively metalated in the 3-position. In papers concerning directed metalation reactions, Slocum et al.^{49,50} reported that 5-trimethylsilyl-*N,N*-dimethyl-2-thiophenesulphonamide⁴⁹ and 5,*N,N*-trimethyl-2-thiophenamine⁵⁰ were also metalated in the 3-position by excess *n*-butyllithium. (See 2.4.)

It was known, from work by Gronowitz et al.,^{15,51} that several β -thienyllithium derivatives rearranged to the more thermodynamically stable α -thienyllithium derivatives if one or both of the α -positions were unsubstituted or substituted with bromine. These rearrangements were dominant at temperatures in



excess of -70°C . Thus, they might compete with the ring-opening reaction making it difficult to interpret the results. By the use of a methyl group or groups in the α -positions it should be possible to avoid such "trans metalations".

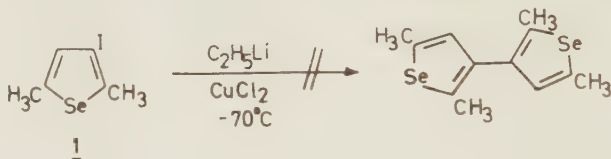
The mechanism of the ring-opening reaction was also considered of interest. Consequently some kinetic measurements were performed together with detailed reaction product analyses, at least in some cases.

In sum, the aim of this work was to investigate the scope and limitations of the ring-opening reaction of 3-lithium heterocycles, with special regard to the thiophenes.

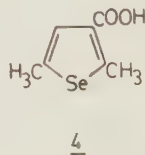
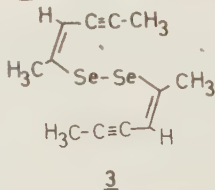
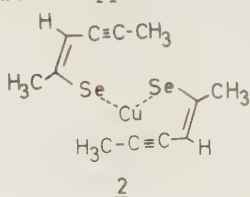
2. RING-OPENING REACTIONS

2.1.1 Ring-opening of 2,5-dialkyl-substituted 3-lithium heterocycles

In the first observation of the ring-opening reaction of 3-lithium heterocycles in this work, 2,5-dimethyl-3-iodoselenophene^{1,2} (1) was used together with ethyllithium in ether at -70°C . These conditions had previously been used in the thiophene series to prepare 2,5-dimethyl-3-thienyllithium.⁵² It was intended to treat the expected 2,5-dimethyl-3-selenienyllithium with cupric chloride so as to obtain 2,2',5,5'-tetramethyl-3,3'-biselenienyl.¹ The corresponding bithienyl derivative had been prepared by an analogous route.⁵² However, no biselenienyl derivative could be detected in the selenophene experiment.



Instead, an ether-soluble oil was obtained that according to combined vpc-ms analysis contained 2,5-dimethylselenophene and an acetylenic compound ($\text{C}\equiv\text{C}$ 2220 cm^{-1} , $m/e = 318$, 2 Se). A solid substance was also isolated which was insoluble in all solvents tried. Its mass spectrum indicated the presence of copper (the parent ion $m/e = 381$ lost 63 to $m/e = 318$) and of two selenium atoms. When this substance was treated with conc. ammonium hydroxide, an oil was formed and a blue colour appeared. This also indicated the presence of copper ion. The oil was taken up in petroleum ether (60-80) and it was shown by combined vpc-ms analysis to mainly consist of the acetylenic compound with $m/e = 318$. It may be suggested that the solid compound could be a copper selenolate such as 2 which was oxidized to the di-



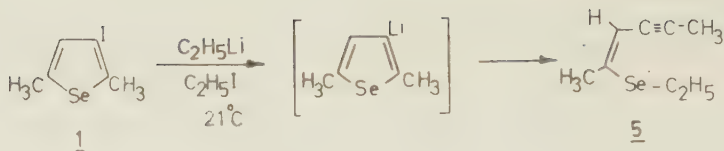
selenide 3 ($m/e = 318$) upon contact with air.⁷⁴ No further attempts were made to more thoroughly examine this reaction.

By trapping 2,5-dimethyl-3-selenienyllithium with carbon dioxide it should be possible to demonstrate its existence. When 2,5-dimethyl-3-iodoselenophene (1) again was treated with ethyllithium at -70°C . for 5 minutes, no selenophenecarboxylic acid was detected after carbonation of the reaction mixture, which made it somewhat doubtful that the lithiumselenophene was present at all⁸ (cf. 2.8.1). The main part of the neutral fraction was 2,5-dimethylselenophene, but minor amounts of other compounds were also present, among which one or more were acetylenes ($\text{ir } 2220 \text{ cm}^{-1}$). However, by lowering the reaction temperature to -110°C (liq. N_2), a 51 % yield of 2,5-dimethyl-3-selenophenecarboxylic acid⁵³ (4) was obtained after carbonation.⁸ These results indicated the existence of 2,5-dimethyl-3-selenienyllithium, which evidently ring-opened rapidly at temperatures around -70°C .

In another experiment the reaction mixture (prepared as described above) was hydrolyzed after having reached room temperature. Now a 50 % yield of (Z)-2-ethylseleno-2-hexen-4-yne (5) and also 2,5-dimethylselenophene (10 %) could be isolated. Vpc analysis of the crude product showed two peaks originating from these compounds in the proportions 75 to 25 respectively. No other peaks larger than .1 % were detected, which means that the Wurtz-Fittig^{*} reaction between ethyl iodide and the aryllithium, forming 3-ethyl-2,5-dimethylselenophene, did not seriously interfere nor did trans metalations of the kind mentioned on p 15.

By adding the ethyllithium rapidly to 1 at room temperature directly and then adding an excess of ethyl iodide to the reaction mixture, it was possible to obtain 5 in a 70 % yield.

* For simplicity the coupling between the aryllithium derivative and the alkyl halide is called the Wurtz-Fittig reaction. More correctly, the coupling represents the last step in this reaction.^{54,62,78,185}



The structure proof for 5 was performed by spectroscopic means together with elemental analysis. Ir absorption at 2220 cm^{-1} indicated a non-terminal acetylene derivative. The ^1H nmr spectrum showed absorptions in the vinyl region ($\delta = 5.58 \text{ ppm}$), two methyl bands at $\delta = 2.12$ and 1.98 ppm and also the presence of an ethyl grouping (a low-field quartet and a high-field triplet). The vinyl band and the two methyl bands were too strongly coupled to allow a first order treatment, and thus no information about the stereochemistry was available from coupling constants without using a computer program. The stereochemical problem was later solved in the case of 3-thienyl- and 3-selenienyllithium²⁶ (cf. 2.2) and independently by Jacobsen³⁰ for some methyl-substituted 3-thienyllithium derivatives.

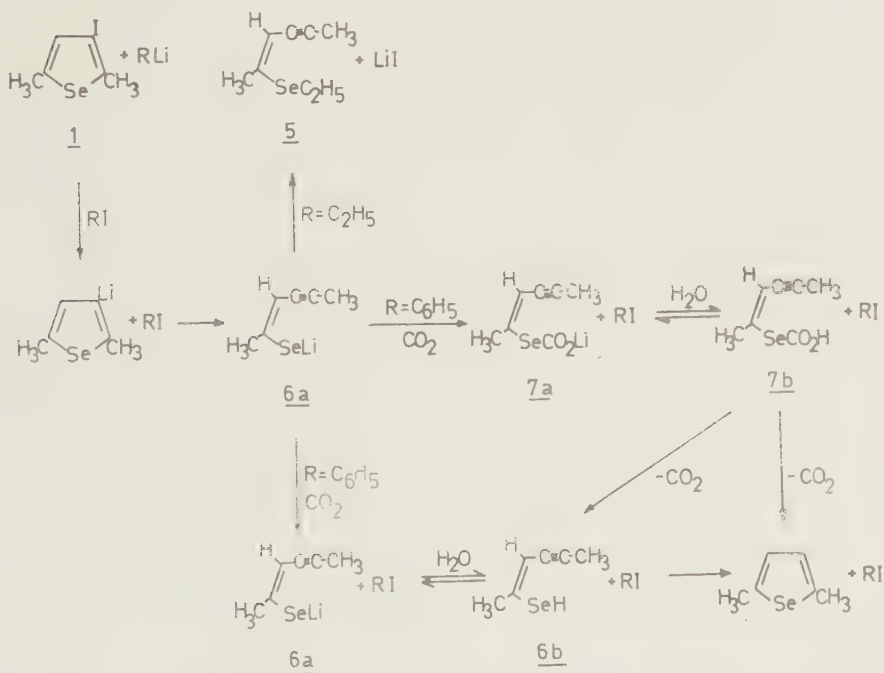
The mass spectrum of 5 showed a molecular fragment at m/e 188 (^{80}Se) which was also the base peak. This was not expected for the isomer of 5, namely 3-ethyl-2,5-dimethylselenophene, which should have a base peak at m/e 173 (loss of methyl) similar to the thiophene analogue.⁹⁸ (The peak at m/e 173 in the spectrum of 5 was only 10 rel %.) See 2.9, Table 3.

Since ethyl iodide was formed in the halogen-metal exchange between 1 and ethyllithium it seems probable that a ring-opening product such as the selenolate 6a (Scheme 3) was alkylated at selenium by ethyl iodide. By using phenyllithium instead of ethyllithium the unreactive iodobenzene would not attack at selenium, and therefore the fate of the selenolate 6a could be further studied. Thus, in such an experiment at room temperature, no carboxylic acid was detected upon carbonation.⁸ However, the neutral ether phase contained equal amounts of 2,5-dimethylselenophene and iodobenzene. This showed firstly, that the halogen-metal exchange had taken place, secondly that ring-opening had completely occurred since no acid was formed, and

thirdly, upon protonation the ring-opening product 6a (and/or 6b) formed 2,5-dimethylselenophene in an intramolecular Michael addition.⁸ To do this 6a (or 6b) must either have the Z-configuration or readily rotate around the formal C-C double bond.



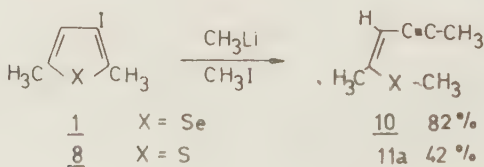
Whether 6a formed the carboxylate 7a with carbon dioxide or not is an open question. If it does, carbon dioxide must be lost from 7a or 7b for 2,5-dimethylselenophene to be formed. This is indicated in Scheme 3.



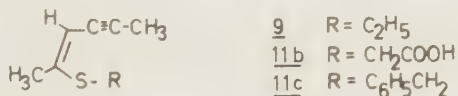
Scheme 3. Reaction paths for 3-iodo-2,5-dimethylselenophene and ethyl- or phenyllithium in ether at room temperature.

Interestingly, 2,5-dimethyl-3-selenienylmagnesium iodide, prepared from 1 and magnesium turnings in ether with a small amount of ethyl iodide present (a modified entrainment method^{55,56}), was quite stable, giving a 52 % yield of 2,5-dimethyl-3-selenophenecarboxylic acid⁵³ (4) upon carbonation.⁸ This stability paralleled that with 2,5-dimethyl-3-thienylmagnesium iodide.⁵⁷ However, it was contrary to the case with 3-benzo[b]thienyl-magnesium bromide, which underwent ring cleavage to ortho-ethynylphenol.⁶

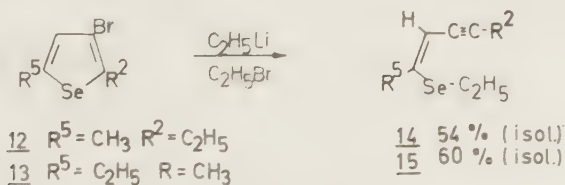
Our attention was naturally focused to the thiophene series. The finding of Wittig and Rings¹⁷ that 3,4-diiodo-2,5-diphenylthiophene gave diphenylbutadiyne after treatment with butyllithium indicated that the ring-opening reaction might be quite general. In the present work, it was shown that 2,5-dimethyl-3-thienyllithium was stable enough for 6 h at -70°C to give a 76 % yield of 2,5-dimethyl-3-thiophenecarboxylic acid after carbonation.⁸ However, when 2,5-dimethyl-3-thienyllithium prepared from 2,5-dimethyl-3-iodothiophene (8) and ethyllithium was kept at room temperature for 4 h together with an excess of ethyl bromide and then hydrolyzed, a 50 % yield of (Z)-2-ethylthio-2-hexen-4-yne^{44a} (9) could be isolated. The spectroscopic properties of 9 were similar to those of 4. (See Experimental Part.) Evidently, 2,5-dimethyl-3-thienyllithium also ring-opened and Scheme 3 could possibly also represent the situation in the thiophene series. It would be favorable to use methyllithium instead of ethyllithium due to the much greater stability of the former,⁵⁸ and also due to the greater reactivity of methyl iodide or bromide in substitution reactions. Thus, both 1 and 8 furnished the corresponding ring-opened products, (Z)-2-methylseleno-2-hexen-4-yne (10) and (Z)-2-methylthio-2-hexen-4-yne (11a), respectively with methyllithium and methyl iodide at room temperature.⁸



In the selenophene case, the crude product was almost pure and crystalline, while in the thiophene case a liquid was obtained which was subjected to distillation during which partial decomposition took place. This fact together with the formation of the "Wurtz-Fittig" product 2,3,5-trimethylthiophene (113) (14 %), explained the low yield of 11a. In contrast to these results, only about 10 % halogen-metal exchange took place when 2,5-dimethyl-3-bromothiophene was the substrate (90 % of the starting material was recovered). Obviously, methylolithium was not the reagent of choice if bromoheterocycles were to be used. Similar results were reported for the reaction between methylolithium and several bromo compounds in the benzene series.⁶⁰ In analogy with the reaction between 1 and phenyllithium, 8 also underwent ring-cleavage. The enyne thiolate could be trapped with dimethylsulphate, ethyl bromoacetate and benzyl chloride to give good yields of the corresponding thioethers 11a (63 %), 11b (58 % after hydrolysis of the initially formed ethyl ester) and 11c⁵⁹ (52 %).



By carrying out the ring-opening with ethyllithium and an excess of ethyl bromide on 3-bromo-2-ethyl-5-methylselenophene (12) and 3-bromo-5-ethyl-2-methylselenophene (13) at room temperature, the isomeric seleno enynes 14 and 15 were obtained in good yields.



In an analogous way, 3-bromo-2-ethyl-5-methylthiophene (16),⁶¹ 3-bromo-5-ethyl-2-methylthiophene (21),⁶¹ 3-bromo-2-*t*-butyl-5-methylthiophene (25),⁶¹ and 3-iodo-5-*t*-butyl-2-methylthiophene (29)⁶¹ gave (*Z*)-2-ethylthio-2-hepten-4-yne (17),

(Z)-3-ethylthio-3-hepten-5-yne (22), (Z)-2-ethylthio-6,6-dimethyl-2-hepten-4-yne (26) and (Z)-3-ethylthio-2,2-dimethyl-3-heptene-5-yne (30), respectively.

Since several by-products were formed in these ring-opening experiments, a more detailed product analysis was undertaken with the compounds 16, 21, 25 and 29. Two experimental conditions were chosen: one with an excess (fivefold) of ethyl iodide (I) and the other without added ethyl iodide (II). All experiments were run with one equivalent of ethyllithium per equivalent of bromoheterocycle at room temperature for 4 h. The results are presented in Scheme 4.

The presence of 2-ethyl-5-n-propylthiophene (24) was shown by comparing its mass spectrum with the literature data (see 2.9) as well as by comparing its retention time (vpc) with that of an authentic sample. In the case of 2-s-butyl-5-methylthiophene (20), only its mass spectrum was taken as evidence for its existence (see 2.9). The mass spectrum of the isomeric 2,3-diethyl-5-methylthiophene (168) was however quite different from that of 20.

The formation of 20 and 24 could possibly be explained by the following reasoning. The original enyne thiolates, from the corresponding ring-opening of 16 and 21, were deprotonated by ethyllithium or the appropriate 3-thienyllithium derivative in the propargylic position, which could be rather acidic.⁶³ Subsequent C-ethylation of the propargylic anion, followed by hydrolysis, should give the thiophene derivatives 20 and 24 (cf. Scheme 3). If the sulphur atoms of the original enyne thiolates were ethylated by ethyl iodide, the propargylic ethylation should give 18 and 23, i.e. the ring-closure should be prohibited by blocking the sulphur atom. Thus one could conclude that the C-alkylation of the propargylic anion could compete rather efficiently with the S-alkylation.

The evidence for the existence of 18 was only its mass spectrum (see 2.9) and its slightly longer retention time compared to 17 (vpc). Compound 23 was however isolated, and gave a satisfactory ¹H nmr spectrum showing the n-propyl grouping. Its mass and ir spectra were also as expected.

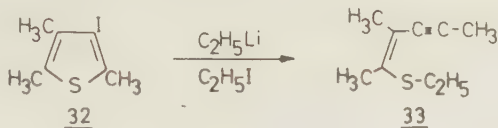
The dehalogenated heterocycles 19 and 27 could arise from the protonation of the corresponding 3-thienyllithium

Starting-material	Cond.	Products	

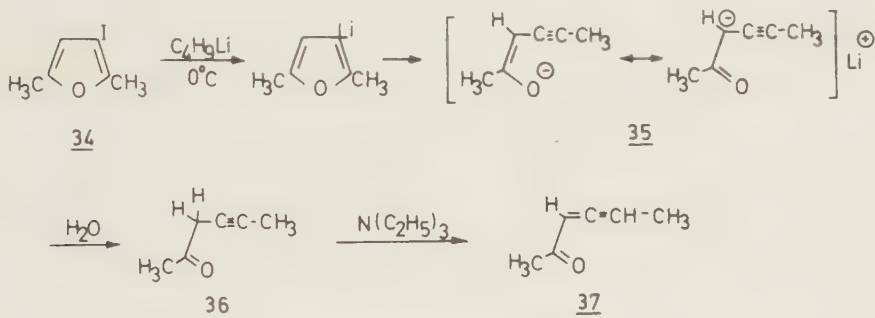
derivatives or their ring-opened isomers (cf. Scheme 3). It did not seem probable that an equilibrium existed between the 3-thienyllithium derivatives and the corresponding enyne thiolates (cf. 2.8.1). In the experiments in which the ethyl iodide concentration was low (II), the amounts of the dehalogenated heterocycles were large. This could be explained by assuming that the S-alkylation of the enyne thiolates was an S_N2 reaction. The alkylation rate would then be dependent upon the ethyl iodide concentration. Substantial quantities of enyne thiolates could therefore still exist in the reaction mixture even after 4 h at room temperature. When water was added these species formed the apparently dehalogenated heterocycles. In the experiments with 29, ring-opening (to 30) and Wurtz-Fittig reaction (to 31) took place to about the same extent. It was later demonstrated that the ring-opening of 5-t-butyl-2-methyl-3-thienyllithium was rather slow (see 2.8.1), which made it possible for the ethyl halide and the thienyllithium derivative to coexist long enough for coupling to become rather extensive. This situation may also arise in other cases where the ring-opening is relatively slow. It has been shown that 2-thienyllithium undergoes Wurtz-Fittig coupling with various alkyl halides.⁷⁸ The presence of 5-t-butyl-3-ethyl-2-methylthiophene (28) was showed by combined vpc-mass spectrometry only. The mass spectrum was rather weak, which made the fragmentation pattern unreliable and the structure is accordingly uncertain.

In order to demonstrate that 3-thienyllithium derivatives with substituents in the 4-position could also be utilized for the synthesis of thioenynes, 4-iodo-2,3,5-trimethylthiophene (32) was treated with ethyllithium and ethyl iodide at room temperature. As expected, (Z)-2-ethylthio-3-methyl-2-hexen-4-yne (33) was formed (50 %). During the progress of this work, Jacobsen³⁰ reported the ring-opening of 4-methyl-3-thienyllithium in the presence of n-butyl bromide which afforded (Z)-1-butylthio-2-methyl-1-buten-3-yne (26 %). These results together with the ring-opening of 2,5-dimethyl-4-phenyl-3-thienyllithium (see 2.3) clearly showed the synthetic possibility of preparing thioenynes with substituents in all positions. It should be pointed out that compounds like the above mentioned thioenynes can not be synthesized by adding thiolates to

diacetylenes, but more elaborate routes must be used. (For possible routes, see Ref. 64.)



2,5-Dimethyl-3-furyllithium also underwent ring-cleavage.²⁶ In this case no alkylated products were formed, but an acetylenic ketone, hex-2-on-4-yne (36) was produced in a 33 % yield. This reaction had to be run at quite a high dilution and under cooling so as to avoid condensation of the enolate 35. Obviously, the low nucleophilicity of the oxygen and the delocalized charge in 35 did not lead to any alkylation.



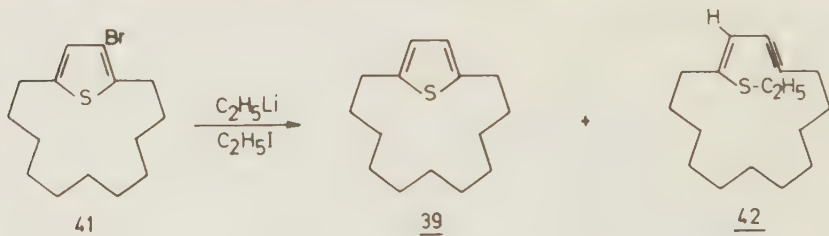
When the reaction mixture was too concentrated, only minor amounts of 36 were detected. In such a case, the main peak on the gas chromatogram originated from a compound with a mass number twice that of 36, indicating dimerization. Compounds with higher mass numbers were also present.

If the reaction mixture containing 36 was allowed to come into contact with base (H_2O , OH^-) for a few minutes, a mixture of 36 and the isomeric 3,4-hexadien-2-one (37) was obtained. By treating 36 with triethylamine in an nmr tube the conversion to 37 could be followed. Acetylenic and allenic ketones similar to 36 and 37 have been synthesized and studied by several authors.⁶⁵

2.1.2 Thiophenophanes

The idea was that if the α -positions of the thiophene ring were connected with a short enough chain it should be impossible to open up the thiophene ring in the way described in this thesis. The strain energy of the cyclic thioenynes would simply become too high. A carbon chain of eight atoms or less should prevent the ring-opening as judged from molecular models, while no considerable strain of the cyclic thioenynes would be expected if the chain were made of ten atoms or more. Thus, suitable starting materials would be 3-bromo-[8](2,5)-thiophenophane (40) and 3-bromo-[11](2,5)-thiophenophane (41) (cf. 3.3.5). Unfortunately, we were not able to obtain 40 through bromination of [8](2,5)-thiophenophane (38)^{66,67} and consequently this part of the question had to be omitted (cf. 3.3.5). However, 41 was obtained through bromination of [11](2,5)-thiophenophane (39) (cf. 3.3.5).

The ring-opening experiment with 41 was carried out with ethyllithium and an excess of ethyl iodide, which afforded a 45 % yield of (Z)-1-ethylthio-1-cyclopentadecen-3-yne (42), together with a 10 % yield of 39 (isolated yields). The neutral ethereal phase from the reaction was shown to contain 39 and 42 in the ratio 20:80 (vpc). In the ^1H nmr spectrum the resonance



of the vinyl proton of 42 appeared at $\delta = 5.48$ ppm as a broad unresolved triplet. A quartet at $\delta = 2.83$ ppm was assigned to the $\text{S}-\text{CH}_2$ grouping. The resonances of the carbon chain protons and the methyl protons of the S -ethyl grouping appeared as two separated bands at $\delta = 2.0$ - 2.5 ppm (four protons) and at $\delta = 1.1$ - 1.7 ppm (21 protons).

A decoupled ^{13}C nmr spectrum of 42 showed the absorptions

of the acetylenic carbons at $\delta = 86.8$ ppm and $\delta = 105.4$ ppm,^{68a} while those of the ethylenic part appeared at $\delta = 114.9$ ppm and $\delta = 155.7$ ppm^{68b} (relative to TMS). The low field resonance of the ethylenic part was assigned to the carbon attached to the sulphur atom, which seemed reasonable in comparison with literature data on 2-methylthiophene, in which the α -carbon resonance appears at lower field than the β -carbon resonance.⁶⁹ The resonance of C-1 in (E)-1-cyanopropene appears at $\delta = 150.8$ ppm and that of C-2 at $\delta = 102.1$ ppm (relative to TMS).^{68b} The facts justify also the suggested assignment. The resonances of the saturated carbon atoms showed up as several lines between $\delta = 22.2$ ppm and $\delta = 43.7$ ppm. It should be pointed out that the latter signal appears at an unusually low field to arise from a sp^3 -hybridized carbon in an aliphatic chain.¹⁸⁸

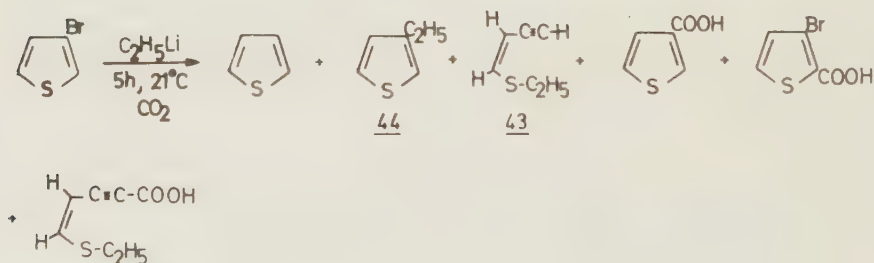
Obviously, the suggestion from the molecular models was verified in this case, which may afford a synthetic route to macrocyclic thioenynes with more than 14 carbon atoms in the ring. The relatively large amount of 39 (20 %) may be explained by assuming a slow ring-opening or a slow alkylation of the enyne thiolate or both. The ring-opening might be slow because of some strain in the aliphatic chain in reality that was not experienced from the model. The alkylation of the thiolate might be slow on the basis of the following possibility. When the cyclic enyne thiolate was allowed to revolve around the sulphur-carbon bond it could be seen from the molecular model that the sulphur atom became located in the center of a cavity if the most favorable arrangement of the molecule was regarded, taking interatomic interactions into account. In such a case the alkylation at sulphur would be sterically hindered, leading to 39 after hydrolysis (see Scheme 3).

2.2 3-Furyl-, 3-thienyl- and 3-selenienyllithium

Both 3-furyl-⁷⁰ and 3-thienyllithium^{71,111} are important reagents for the synthesis of 3-substituted heterocycles. The reaction temperature has almost always been around -70°C where these lithium heterocycles were obviously stable. Moreover, Gronowitz and Moses¹⁵ showed that 3-thienyllithium, prepared at

-70°C , was stable enough at room temperature for 1 h to yield solely 3-thiophenecarboxylic acid upon carbonation. When the period at room temperature was extended to several hours before carbonation, no 3-thiophenecarboxylic acid was obtained, but two other acids, namely 3-bromo-2-thiophenecarboxylic acid and 2-thiophenecarboxylic acid were formed. This "rearrangement" was explained through transmetalation reactions (as shown on p. 15), in which the lithium atom was eventually placed in the most "acidic" position. In an experiment in which 3-thienyllithium in ether was allowed to stand 24 h at room temperature, the above authors obtained an oil, which showed the presence of unsaturated aliphatic compounds in the infrared.

In the present work, 3-thienyllithium (prepared at -70°C) was kept at room temperature for 5 h in the presence of an excess of ethyl bromide before carbonation of the reaction mixture.²⁶ A carboxylic acid mixture was obtained ($\sim 48\%$ yield) containing 85 mol % of 3-thiophenecarboxylic acid, 10 mol % of 3-bromo-2-thiophenecarboxylic acid and 5 mol % of what might be (Z)-1-ethylthio-1-buten-3-yne-4-carboxylic acid (nmr). The earlier observation by Gronowitz and Moses of an unsaturated compound¹⁵ might accordingly have been due to this acid. The neutral fraction was analyzed by vpc and found to contain thiophene, together with ethylthiophene (44) and a small amount of (Z)-1-ethylthio-1-buten-3-yne (43).^{44b} Compound 44 was probably 3-ethylthiophene since its nmr spectrum was identical with that of an authentic sample. The presence of 3-thiophenecarboxylic



acid in the crude product was taken as evidence for the greater stability of 3-thienyllithium toward ring-cleavage than of 2,5-dimethyl-3-thienyllithium, although some ring-cleavage did occur.

When the reaction mixture was instead hydrolyzed, a similar experiment gave a crude product containing 74 % of thiophene, 12 % of 44, 6 % of 3-bromothiophene and 7 % of 43. By adding ethyllithium rapidly to 3-bromothiophene without cooling, and then adding ethyl bromide the amount of 43 rose to 14 % at the expense of thiophene. It proved to be difficult to separate 43 and 3-bromothiophene (tlc), which was present in all crude products, despite a slight excess of ethyllithium (~ 5 %). Therefore 3-iodothiophene was used as a source of 3-thienyllithium. This did not significantly change the product distribution. The results are shown in Scheme 5.

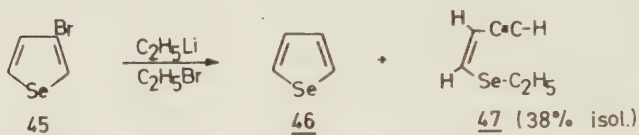
Substrate	Time at -70°C	Time at +21°C		<u>44</u>	Starting material	<u>43</u>
	10 min	5 h	74%	12%	6%	7%
		5 h	65%	13%	8%	14%
		5 h	65%	12%	7%	16%

Scheme 5. Product distribution after hydrolysis of the reaction mixtures between 3-halothiophenes and ethyllithium in ether in the presence of an excess of ethyl bromide (vpc, uncalibrated values).

It seemed reasonable that some of the 3-bromo- or 3-iodothiophene originated from 3-bromo- or 3-iodo-2-thienyllithium formed in a direct metalation of the 2-position, since ethyllithium was added to a solution of the halothiophenes. However, the possibility of a transmetalation of the 3-thienyllithium derivatives should not be overlooked.

Earlier observations of low yields by using 3-selenienyllithium at temperatures around -70°C for the preparation of some 3-selenienyl derivatives⁴⁰⁻⁴² could be caused by a rapid ring-opening of 3-selenienyllithium. However, a 77 % yield of 3-selenophenecarboxylic acid was achieved upon carbonation of

3-selenienyllithium at -70°C .²⁶ Even at -50°C the yield was 58 %. Obviously, the ring-opening of 3-selenienyllithium was slower than that of 2,5-dimethyl-3-selenienyllithium, which paralleled the results in the thiophene series. When 3-selenienyllithium was prepared at -70°C (from 3-bromoselenophene (45)⁴² and ethyllithium in ether), and the reaction mixture was allowed to reach room temperature and kept there for 5 h (excess ethyl bromide), (Z)-1-ethylseleno-1-buten-3-yne (47), and selenophene (46) were formed in the proportions 50:50 (vpc). By performing the entire reaction at room temperature the proportions were 70:27. About 3 % of 45 was also present. The increase



in yield of 47 was analogous to the thiophene case, which indicated that 3-selenienyllithium also underwent reactions that competed with the ring-opening reaction at temperatures between -70°C and room temperature (e.g. trans-metalations or reaction with the solvent and the ethyl halide⁶²).

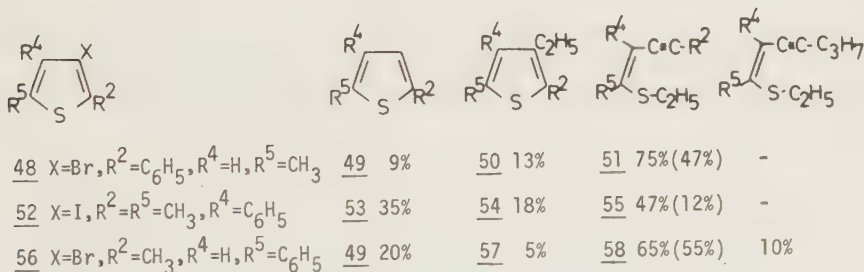
Attempts to isolate well defined products from the decomposition of 3-furyllithium at -10° - $+21^{\circ}\text{C}$ were unsuccessful. Only brown solids were obtained, the ir spectra of which showed very few absorptions (no acetylenic ones).

The ^1H nmr spectra of 43 and 47 were similar, and the presence of two vicinal vinylic protons allowed the assignment of configuration from their mutual coupling constants; $J_{\text{HC}=\text{CH}} = 9.80$ and 9.70 Hz for 43 and 47, respectively. Since vinylic protons in a cis arrangement usually showed coupling constants in the range of 5-14 Hz and those in a trans arrangement 11-19 Hz⁷² it was tentatively suggested that 43 and 47 had the (Z)-configuration.

The much faster ring-cleavage of 2,5-dimethyl-3-selenienyllithium and 2,5-dimethyl-3-thienyllithium than of 3-selenienyllithium and 3-thienyllithium, respectively pointed to an enhancement of this reaction by +I substituents except when steric demands dominated (see 2.8.1 and 2.8.3).

2.3 Phenyl-substituted 3-thienyllithium derivatives

If the above hypothesis were correct, concerning the influence of the inductive effect of different substituents upon the ring-opening of 3-thienyllithium derivatives, one would believe that phenyl groups (-I, +M substituent) in the ortho positions to lithium should slow down the ring-opening rate, while no such influence would be noticed if the phenyl group were in the meta position. In order to investigate these matters, 3-bromo-5-methyl-2-phenylthiophene (48), 3-iodo-2,5-dimethyl-4-phenylthiophene (52) and 3-bromo-2-methyl-5-phenylthiophene (56) were treated with ethereal ethyllithium followed by ethyl bromide at room temperature (+21°C). The reaction mixtures were then hydrolyzed after 4 h. As can be seen in Scheme 6 the lithium derivatives of all these substances underwent ring-cleavage. Obviously the phenyl group was not capable of preventing it. However, the large amounts of dehalogenated heterocycles in the case of 52 and 56 indicated that the corresponding thienyllithium derivatives were rather stable or that the enyne thiulates were slowly alkylated. It is also possible that ethyl bromide was attacked by the thienyllithium derivatives in an elimination reaction resulting in the formation of ethene, lithium bromide and the dehalogenated heterocycle.⁶² This could become more pronounced with "long-lived" 3-thienyllithium derivatives.



Scheme 6. Product analysis of the reaction between different phenyl-substituted 3-halothiophenes and ethyllithium in the presence of a fivefold excess of ethyl bromide. Reaction conditions; 4 h at +21°C, then hydrolysis. (Uncalibrated vpc values.) Figures in parentheses represent isolated yields.

In order to obtain accurate information as to whether the ring-opening reaction was slow in the above-mentioned cases, kinetic measurements were performed in the absence of alkylating agents in the reaction mixture (cf. 2.8.1 and 2.8.3).

For preparative purposes, the ring-opening of 48 and 56 with ethyllithium seems useful, since 47 % and 55 % yields of 51 and 58 could be isolated. However, it was more difficult to isolate 55 since its properties were too similar to those of some of the by-products. The isolated yield in this case was 12 %. The ring-opening of 52 was made of preparative value by using phenyllithium as metal-introducing agent and then trapping the enyne thiolate with dimethylsulphate. Such experiments also gave good yields of enyne-methylthioethers in the cases of 3-iodo-5-methyl-2-phenylthiophene (59) and 3-iodo-2-methyl-5-phenylthiophene (61) (Scheme 7) (cf. 2.8.1).



<u>59</u>	$R^2 = C_6H_5, R^4 = H, R^5 = CH_3$	<u>60</u>	69 %
<u>61</u>	$R^2 = CH_3, R^4 = H, R^5 = C_6H_5$	<u>62</u>	50 %
<u>52</u>	$R^2 = R^5 = CH_3, R^4 = C_6H_5$	<u>63</u>	63 %

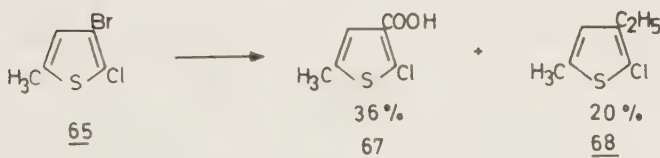
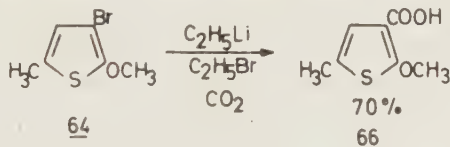
Scheme 7. Isolated yields of enyne-methylthioethers when some phenyl-substituted 3-iodothiophenes were treated with phenyllithium at +21°C for 4 h, followed by dimethylsulphate.

2.4 Chloro-, methylthio- and methoxy-substituted 3-lithium heterocycles

Since the relatively weak -I phenyl substituent (F-parameter = 0.139 according to Swain and Lupton⁷⁵) did not completely stop the ring-cleavage but only slowed it down to some extent, the next step was to introduce some more powerful -I substituents such as chloro, methoxy, and methylthio (F-parameters⁷⁵ 0.690, 0.413 and 0.332, respectively) in the position ortho to lithium.

One should bear in mind that these groups also possess free electron pairs, which may act as electron donors (Lewis bases) to electron deficient centers (Lewis acids), thus stabilizing the lithium compounds towards ring-opening. (For further discussion see 2.8.2.)

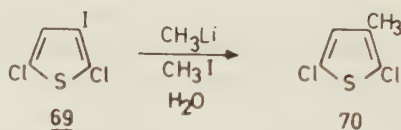
Both 3-bromo-2-methoxy-5-methylthiophene (64) and 2-chloro-3-bromo-5-methylthiophene (65) gave the corresponding carboxylic acids (66 and 67) after ethyllithium treatment at room temperature followed by carbonation. In the latter case, the Wurtz-Fittig reaction was rather prominent, giving rise to 20 % of 2-chloro-3-ethyl-5-methylthiophene (68), which was increased to 51 % when the reaction mixture was kept at room temperature over night and then hydrolyzed. Earlier, Sicé⁴⁸ metalated 2-methoxy-5-methylthiophene with butyllithium at room temperature and isolated a 50 % yield of 66 after carbonation. This result indicated that 2-methoxy-5-methyl-3-thienyllithium was quite stable under these conditions. However, it was quite likely that the ring-opened product, if it were formed, would have escaped detection since no alkylating agent was present.



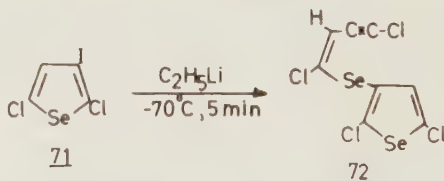
In the experiments performed in this work no acetylenic compounds could be detected, despite the presence of an alkylating agent, which indicated that neither 2-methoxy-5-methyl-3-thienyllithium nor 2-chloro-5-methyl-3-thienyllithium underwent ring-cleavage. Upon attempted metalation of 2-methyl-5-methoxy-selenophene¹⁵³ (131), it was not possible to isolate any carboxylic acid after carbonation. Red elemental selenium was deposited from the aqueous extract, which should have contained

acidic products.

In an experiment in which 2,5-dichloro-3-iodothiophene (69) was treated with methyl lithium and methyl iodide at room temperature for 2 h followed by hydrolysis, only 2,5-dichloro-3-methylthiophene (70)⁷⁷ was formed (60 %; cf. Ref. 78).



The Wurtz-Fittig reaction was now even more pronounced and it could be argued that the chlorine atoms might speed up this reaction, thus consuming all of the 2,5-dichloro-3-thienyllithium before any ring-opening could occur. By using phenyllithium instead of methyl lithium and quenching the reaction with dimethylsulphate, it could be shown that no ring-opening had occurred after 2 h at room temperature, and that 70 was formed in 99 % yield (vpc). One could now expect 2,5-dichloro-3-selenienyllithium to be more stable toward ring-opening than 3-selenienyllithium and 2,5-dimethyl-3-selenienyllithium. Surprisingly, this was not the case. Even at -70°C and after 5 minutes, an acetylenic derivative was formed in 50-70 % yield (nmr) when 2,5-dichloro-3-iodoselenophene (71) was treated with ethyllithium. Since this acetylenic derivative was too labile, it did not survive isolation attempts (tlc).



The following spectroscopic data for the crude product indicated that the substance was 2,5-dichloro-3-selenienyl 1,4-dichloro-1-buten-3-ynyl-1 selenide (72):

1) By using the direct inlet system of the mass spectrometer the most heavy fragment appeared at m/e 398, the isotopic composition of which indicated a content of 4 chlorine atoms and

2 selenium atoms. The simulated mass distribution of $C_8H_2Se_2Cl_4$ was almost identical with the experimental one (see 2.9).

2) Absorptions at 2180 cm^{-1} (strong) and 2260 cm^{-1} (weak) were observed in the infrared. The absence of absorptions around 3200 cm^{-1} indicated the substance to be a non-terminal acetylene.

3) A 1H nmr spectrum showed the absorption of the starting material and two singlets at $\delta = 6.96\text{ ppm}$ (aromatic) and $\delta = 6.10\text{ ppm}$ (vinylic) with the intensities 1:1. No lines in the region of terminal acetylenic protons were observed.

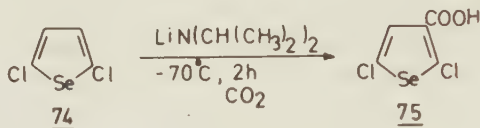
4) ^{77}Se nmr. The decoupled spectrum of the crude product showed the peak originating from the starting material (see below) together with one line at 2480 Hz lower field and one line at 2800 Hz higher field than the selenium resonance of selenophene, which was used as a reference. The low-field line was well inside the region where the aromatic selenium resonance was expected to appear.⁷⁹ The high-field line was on the borderline between the aromatic selenium and the selenide resonances,⁷⁹ which was also as expected for the side-chain selenium in compound 72 (see below). The non-decoupled spectrum showed two doublets; $J_{1Se,4H} = 2.4\text{ Hz}$, and $J_{Se\text{ side-chain},H\text{ vinylic}} = 9.0\text{ Hz}$.

Since the crude product contained 71 a decoupled spectrum of this compound was recorded. A single line appeared at 2675 Hz lower field than the reference. The non-decoupled spectrum showed a doublet with a spacing of 2.0 Hz (i.e. $J_{Se,4H} = 2.0\text{ Hz}$). In order to estimate where the absorption of the side-chain selenium would appear a decoupled spectrum of 2,5-dichloro-3-methylselenoselenophene (73) (see 3.3.4) was recorded. The aromatic selenium absorption was at 2245 Hz lower field and the side-chain selenium absorbed at 8315 Hz higher field than the reference. The non-decoupled spectrum showed that the low-field band was a doublet ($J_{1Se,4H} = 2.40\text{ Hz}$), and that the high-field band was a doublet with fine structure ($J_{3Se,CH_3} = 12\text{ Hz}$, $J_{3Se,4H} = 0.4\text{ Hz}$). Now, since the side-chain selenium in compound 72 besides being attached to an aromatic ring was also in a vinylic position, it could be expected to give a resonance signal at lower field than that of the methylseleno group in 73.

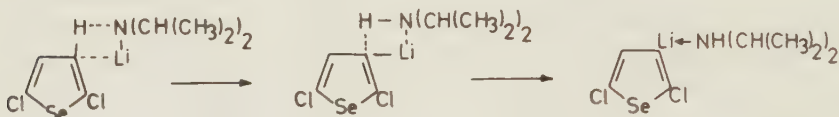
Since the ring-opening tendency of the 3-selenienyllithium derivatives did not parallel the situation in the thiophene series, it is tempting to suggest that the mechanisms are

different at least in the above case. It is possible that the ring-opening of 2,5-dichloro-3-selenienyllithium is of radical nature, which possibly might explain the rapid formation of 72.

When 2,5-dichloroselenophene^{80a} (74) was metalated with lithium diisopropylamide at -70°C (2 h), a 78 % yield of 2,5-dichloro-3-selenophenecarboxylic acid (75) was obtained after carbonation.



This result indicated a stabilizing effect of diisopropylamine which was formed in the reaction. Complex formation as formulated below may be suggested:

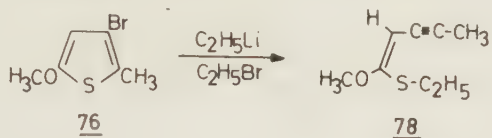


It should be pointed out that since diisopropylamine is formed at the reaction center, the proximity of the amine to the lithium atom could be very favorable for complexation (it was not necessary to displace a solvent molecule).

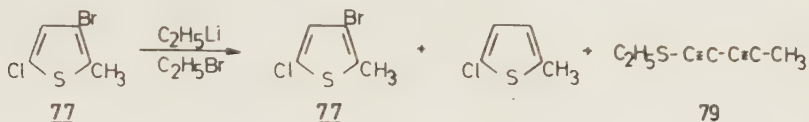
The inductive effect and the electron donor capacity of the chloro and methoxy groups would have less stabilizing influence on the thienyllithium derivatives if these groups were in the "meta" position relative to lithium.

Indeed, both 3-bromo-5-methoxy-2-methylthiophene (76) and 5-chloro-3-bromo-2-methylthiophene (77) underwent ring-cleavage after treatment with ethyllithium. The ring-opening of 5-methoxy-2-methyl-3-thienyllithium was followed by vpc and it was shown that the reaction proceeded rather slowly. Even after 4 h at $+21^{\circ}\text{C}$ the peak originating from (Z)-1-ethylthio-1-methoxy-1-penten-3-yne (78) was still growing larger. Since a precipitate, probably 5-methoxy-2-methyl-3-thienyllithium, was formed immediately when ethyllithium and 76 were mixed the reaction became heterogeneous. This could be responsible for

the apparently slow ring-opening (cf. 2.8.1). In order to make the reaction homogeneous, a small amount of hexamethylphosphoroustriamide (HMPA) was added to the reaction mixture. In this way, a 33 % yield of 78 was obtained and the ring-opening was complete in less than 2 h.



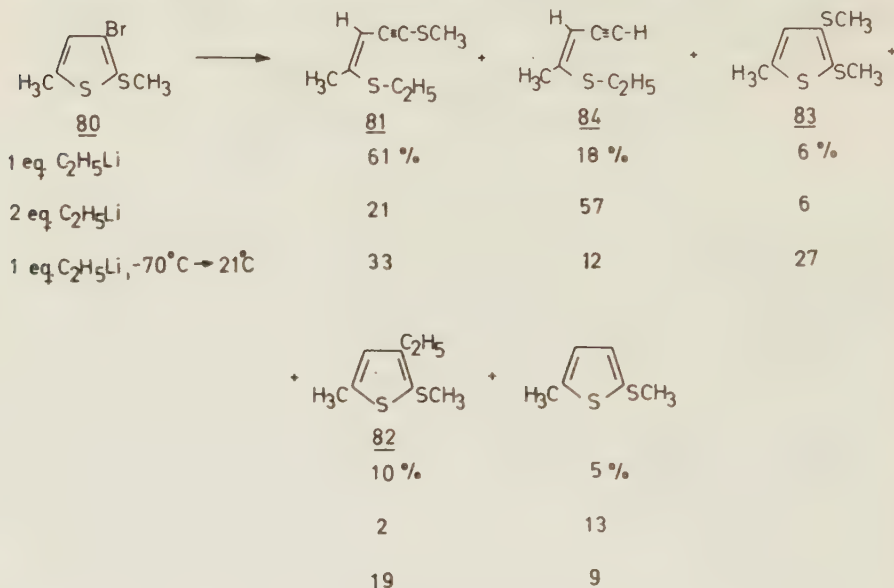
The ring-opening of 2-chloro-5-methyl-3-thienyllithium appeared to be more complex. As much as 21 % of the starting material and 42 % of 2-chloro-5-methylthiophene were present in the crude product, together with 37 % of 1-ethylthio-1,3-pentadiyne⁸¹ (79) (uncalibrated vpc values).



The following reasoning seems to account for this result: 5-chloro-2-methyl-3-thienyllithium is rapidly formed when ethyllithium is added to 77. A subsequent ring-opening should yield lithium (Z)-1-chloro-1-penten-3-yne-2-thiolate, which should be able to eliminate hydrogen chloride in the presence of base. The base could of course be either ethyllithium or the thienyllithium derivative, or both, but the results implied that ethyllithium was the base, since a substantial amount of the starting material was recovered.

It was of interest to find out whether the methylthio group would behave as the methoxy group, or if its weaker -I effect would also permit ring-opening when it was in the position ortho to lithium. The latter was shown to be the case. Thus, 3-bromo-5-methyl-2-methylthiothiophene^{82a} (80) gave mainly (Z)-2-ethylthio-5-methylthio-2-penten-4-yne (81) after ethyllithium-ethyl bromide treatment at room temperature. However, not only the "usual" reaction products such as 2-methyl-5-methylthiothiophene⁸³, and the "Wurtz-Fittig product", 3-ethyl-5-methyl-2-

methylthiophene (82), were present in the crude product, but also 5-methyl-2,3-bis-methylthiophene (83) and what is believed to be (Z)-2-ethylthio-2-penten-4-yne (84) (Scheme 8).



Scheme 8. Reaction product analysis of the reaction between 3-bromo-5-methyl-2-methylthiophene (80) and ethyllithium in the presence of ethyl bromide. Reaction time at +21°C; 4 h, then hydrolysis; uncalibrated values.

(No serious attempts to isolate 81 or 84 were made but small enriched samples were obtained (tlc) showing the expected spectroscopic properties.) When two equivalents of ethyllithium were used compound 84 was the main component which made it likely that ethyllithium attacked the sulphur atom of the acetylenic methylthio group of 81 or that of lithium 5-methylthio-2-penten-4-yne-2-thiolate (as a nucleophile).⁷⁶ It also seemed likely that 5-methyl-2-methylthio-3-thienyllithium acted as a nucleophile similar to ethyllithium, which would explain the formation of the bis-methylthiophene derivative 83. Some further evidence that this could be the case was obtained from an experiment in which the halogen-metal exchange was per-

formed at -70°C , whereupon the reaction mixture was allowed to reach room temperature. In this case, the amount of 83 increased. This indicated that the thienyllithium derivative had time enough for the nucleophilic substitution at sulphur to become rather extensive at temperatures where the ring-opening was slow. If 83 was formed only through a nucleophilic attack on the acetylenic methylthio derivative (Scheme 8) the amount of 83 would be less than or equal to the amount of 84. A thermal decomposition of 84 in the injector of the gas chromatograph might be responsible for the actual values, since no calibration was made, and it is well-known that terminal acetylenes are sensitive to heat.^{43,84a}

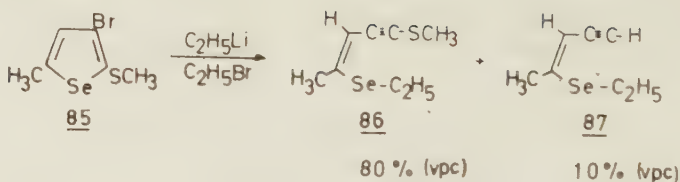
From a preparative point of view, this reaction was apparently too complex to be of value. Besides, 81 could probably be prepared by the addition of ethylthiolate to 1-methylthio-1,3-pentadiyne since methylthiolate was reported to add so as to yield the methylthio homologue of 81.^{84b}



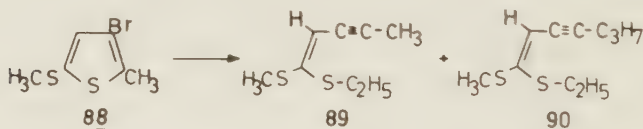
Gol'dfarb et al.^{82a} demonstrated that 5-methyl-2-methylthio-3-thienyllithium was stable enough at 0°C to give a 42 % yield of 3,5-dimethyl-2-methylthiothiophene upon treatment with dimethylsulphate after one hour. The relatively low yield could be indicative of a ring-opening reaction, but no report of the formation of acetylenes was made. It was also possible to metalate 2-methyl-5-methylthiothiophene in the 4-position with butyllithium at room temperature in low yield.^{82b} These results indicated, however, that 5-methyl-2-methylthio-3-thienyllithium was considerably more stable toward ring-opening than the reference substance 2,5-dimethyl-3-thienyllithium (see 2.8.1).

In the selenophene series, the reaction with one equivalent of ethyllithium at room temperature was cleaner. Thus a 44 % yield of (Z)-2-ethylseleno-5-methylthio-2-penten-4-yne (86) could be isolated when 3-bromo-5-methyl-2-methylthioselenophene (85) was the substrate. Combined vpc-ms analysis showed that also in this case the methylthio group of 86 could be lost, giving about 10 % of (Z)-2-ethylseleno-2-penten-4-yne (87). (Four other unidentified compounds amounting to less than 10 %

were also formed.)



As expected 3-bromo-2-methyl-5-methylthiothiophene (88) gave (Z)-1-ethylthio-1-methylthio-1-penten-3-yne (89) in 70 % yield (vpc) when treated with ethyllithium and ethyl bromide at room temperature. Two other compounds were also formed, both with mass number 200. As judged from the fragmentation pattern the compound with the longest retention time was 1-ethylthio-1-methylthio-1-hepten-3-yne (90) (25 %) (see 2.9, Table 3).



Attempted preparative vpc of the crude mixture resulted in extensive decomposition. It was indicated by nmr that the small amount obtained of what was believed to be pure 89 was actually a 50:50 mixture of the Z- and E-isomers since almost every signal was a doublet. Obviously the high temperature in the gas chromatograph (190°C) caused a thermal isomerization. Barriers to rotation around the carbon-carbon double bond of some ketene mercaptals have been measured by Sandström et al.⁸⁵ and shown to be quite high although accessible for nmr measurements. These substances were all substituted with groups exerting a push-pull effect.

Once more, the ring-opening of the selenienyllithium compounds was shown to produce a more uniform crude product. Thus 3-bromo-2-methyl-5-methylthioselenophene (92) gave an 80 % yield of 90 % pure (Z)-1-ethylseleno-1-methylthio-1-penten-3-yne (93) after treatment with ethyllithium and ethyl bromide.

These kinds of acetylenic mixed ketenemonothioacetals 78,



ketenedithioacetals 89 and ketenethio-selenoacetals 93 with controlled configuration do not seem to have been previously described in the literature. A possible route to this class of compounds would be the addition of carbon disulphide to a propargylic anion followed by the desired alkylating agents. The stereochemistry would, however, be exceedingly difficult to control. One would also be restricted to symmetrical propargylic compounds. Consequently, at present the ring-opening reaction seems to be the only realistic route to this type of substances.

It does not seem possible to prepare ketenethio-selenoacetals with E-configuration by using e.g. 3-bromo-2-methyl-5-methylselenothiophene and ethyllithium. Gol'dfarb et al.^{86a} have shown that the methylseleno function was displaced by butyllithium even at -70°C to give 3-bromo-2-methyl-5-thienyllithium and butylmethyl selenide. Methyl phenyl selenide^{86b} and diphenyl selenide^{86c} are cleaved by butyllithium in ether at or above room temperature. Seebach and Peleties^{86d} have recently examined the reaction of e.g. tris-phenylselenomethane with butyllithium and found that both deprotonation of the acidic hydrogen and cleavage of the Se-CH bond took place.

Regarding the ring-opening of the methylthio heterocycles, it could be concluded that no appreciable stabilization was noticed when the reactions were run at room temperature. This could be attributed to the weak -I effect of the methylthio group compared with that of the methoxy and chloro substituents. Gol'dfarb's results concerning the stability of 5-methyl-2-methylthio-3-thienyllithium⁸² clearly showed, however, that a methylthio group in the position ortho to lithium rendered the molecule more stable toward ring-opening than did a methyl group.

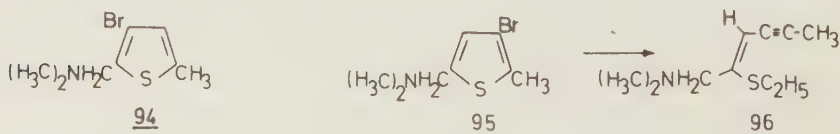
2.5 N,N-Dimethylaminomethyl-substituted 3-thienyllithium derivatives

The dimethylaminomethyl group would probably stabilize a 3-thienyllithium derivative only by the use of its non-bonded electrons, since the inductive effect would be small and positive (cf. 2.8.2). The observation that 2,5-dichloro-3-seleni-
enyllithium was somewhat stabilized in the presence of an amine provided support for the assumption that e.g. 2-N,N-dimethylaminomethyl-5-methyl-3-thienyllithium would be resistant toward ring-opening.

As mentioned previously, Slocum and Gierer⁴⁹ showed that 5,N,N-trimethyl-2-thenylamine was metalated in the 3-position by n-butyllithium at room temperature. The lithium compound was trapped with benzophenone which gave a 65 % yield of diphenyl-(2-N,N-dimethylaminomethyl-5-methyl-3-thienyl)methanol (Scheme 9). The possibility for the lithium compound to ring-open was not mentioned.

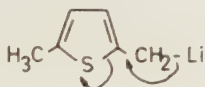
It was, however, shown by nmr spectroscopy in this work that no vinylic hydrogen absorption was present even after 12 h at room temperature in an experiment in which 2-N,N-dimethylaminomethyl-5-methyl-3-thienyllithium was sealed in a nmr tube and the vinyl region was scanned at different times. The thienyllithium derivative was prepared through a halogen-metal exchange between 3-bromo-5,N,N-trimethyl-2-thenylamine (94) and ethyllithium in ether. In a parallel experiment, it was shown that only 5,N,N-trimethyl-2-thenylamine¹⁸² was formed upon hydrolysis after 4 h. The Wurtz-Fittig reaction evidently did not interfere.

On the other hand, ring-opening did take place when the N,N-dimethylaminomethyl function was situated in the 5-position. Thus 3-bromo-2,N,N-trimethyl-5-thenylamine (95) gave about a 50 % yield of (Z)-1-N,N-dimethylamino-2-ethylthio-2-hexen-4-yne (96) when treated with ethyllithium and ethyl bromide at room temperature for 4 h.



2.6 2-Thenyllithium derivatives

The hitherto described ring-opening reactions could be formulated as 1,2-elimination reactions. Instead of placing a lithium atom in the β -position of the heterocyclic ring, it should be possible to achieve ring-opening from the side-chain in e.g. 2,5-dimethylthiophene by placing the lithium atom in the thenylic position.



This type of 1,2-elimination had previously been observed by Gaertner for 2-benzo[b]furylmagnesium chloride and 3-methyl-2-benzo[b]thenylmagnesium chloride.¹⁰ During the course of this work, Meyers et al. reported the ring-opening of some 2-lithio-methylthiazole derivatives.³⁴

Previously, Gaertner described the preparation and some reactions of 2-thenylmagnesium chloride.⁹³ This compound was synthesized by the use of 2-thenyl chloride and magnesium in a special reactor; otherwise the yield was low. Upon reaction with diverse reagents, such as carbon dioxide and formaldehyde, mixtures of the 3-substituted 2-methylthiophenes and the 2-thenyl derivatives were formed. This was explained by assuming a kind of allylic rearrangement. As no signs of ring-opening were reported, it must be concluded that 2-thenylmagnesium chloride was stable since Gaertner was obviously aware of the ring-opening possibility.

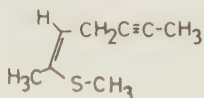
Some years ago, 2,5-dimethylthiophene was metalated by the 1:1 complex between butyllithium and TMEDA in a mixture of ether and hexane in these laboratories.⁹⁴ After carbonation of the reaction mixture an 8 % yield of 3-carboxyl-5-methyl-2-thienyl-acetic acid (97) was isolated. Most of the starting material was recovered. Obviously, metalation took place in the side-chain as well as in the 3-position in an unknown order.

In the light of the results on the ring-opening reaction of 2,5-dimethyl-3-thienyllithium it could be presumed that this reaction might be in part responsible for the low yield in the

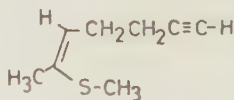
above mentioned metalation, but ring-opening from the side-chain was also possible. Since the metalation was performed at the reflux temperature of a mixture of hexane and ether for two hours, the heterocyclic lithium compounds, whichever they were, were rather resistant toward ring-opening. That any acid was isolated at all might have been due to the precipitation of some lithiated heterocycle which made the reaction heterogeneous. It was shown in the present work that the precipitation of 2,5-dimethyl-3-thienyllithium slowed down the ring-opening reaction considerably (cf. 2.8.1).

When the metalation of 2,5-dimethylthiophene was reinvestigated it was found that a mixture of two acids was formed in 8 % yield after carbonation, namely 2,5-dimethyl-3-thiophene-carboxylic acid (25 %) and the above mentioned thienylacetic acid derivative 97 (75 %).²⁸

When the reaction mixture was treated with ethyl bromide instead of solid carbon dioxide, a crude product was obtained that showed acetylenic frequencies in the infrared at 3300 cm^{-1} , 2210 cm^{-1} and 2080 cm^{-1} . Combined vpc-ms analysis revealed that besides 2,5-dimethylthiophene (80 %), 9 other components were present ranging in mass number from 140 to 168. Also a ^1H nmr spectrum of the crude product (most of the 2,5-dimethylthiophene was removed by evaporation) indicated the presence of unsaturated compounds; several lines at $\delta = 5.25\text{--}5.70\text{ ppm}$ indicated the presence of vinylic protons and a line at $\delta = 3.1\text{ ppm}$ could originate from an acetylenic proton. No absorptions were found in the aromatic region. Signals were also observed in the methyl region. The component with mass number 140 could have the structure 98 or 99.



98

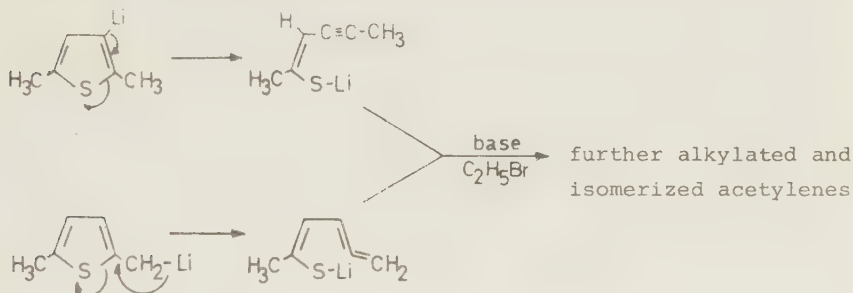


99

These compounds could be further alkylated in the basic mixture, giving rise to the compounds with mass numbers 154 and 168 (see Experimental Part). Some fully alkylated thiophene derivatives such as tetramethylthiophene and trimethyl-ethyl-

thiophene could also be present. No attempts were made to isolate and identify any of the components.

Based on these data, it was quite obvious that ring-opening had occurred and could partly be responsible for the low yield in the carbonation experiment. It was, however, impossible to determine whether it was the 2-thienyllithium or the 3-thienyllithium derivative that had ring-opened. In both ways acetylenic derivatives could be formed, which in the basic medium could be isomerized⁹⁵ and further alkylated. Nor was it



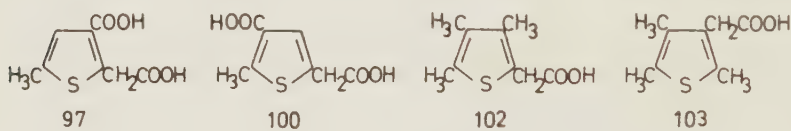
possible to deduce which of the two possible positions were metalated first, since in the carbonation experiment an "allylic rearrangement" of 5-methyl-2-thienyllithium (similar to that of 2-thienylmagnesium chloride⁹³) could give 2,5-dimethyl-3-thiophenecarboxylic acid. The recovery of about 80 % of the starting material indicated a slow metalation of 2,5-dimethylthiophene by the alkyllithium-amine complex.

During the progress of this work it was reported by Meth-Cohn et al.⁹⁶ that the yield of acids could be increased to 16 % if only hexane was used as a solvent and if the reaction was performed at room temperature for 2 h. Moreover, a twofold excess of the 1:1 complex between n-butyllithium and TMEDA was used.

In contrast to the results obtained in these laboratories, the above authors claimed to have found 3-carboxy-2-methyl-5-thienylacetic acid (100) as the main product in their experiment. However, by repeating their experiment it was shown that no such acid was formed, as was evident from comparison with an authentic sample (see 3.3.3, Scheme 14). The trimethylsilyl esters of 97

and 100 had quite different retention times (vpc) and no trace of the silyl ester of 100 was found in the reaction product. Three components were observed in the proportions 2:8:90. The latter two were the silyl esters of 2,5-dimethyl-5-thiophene-carboxylic acid and 97 respectively. The first one was not identified.

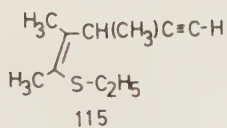
In order to find out if ring-opening could occur from the side-chain, tetramethylthiophene (101) was metalated with the ethyllithium-TMEDA complex in refluxing ether. After 2 h, 1/3 of the reaction mixture was carbonated, which gave a 5 % yield of 3,4,5-trimethyl-2-thienylacetic acid (102). It could not immediately be excluded that metalation had taken place in the β -methyl groups, and that the acid consequently could be 2,4,5-trimethyl-3-thienylacetic acid (103). This acid was, however, synthesized (see 3.3.1, Scheme 10) and shown to be different from the acid in the carbonation experiment. It also seemed reasonable to assume that the protons in the α -methyl groups should be more prone to exchange with lithium than those in the β -methyl groups due to some directing influence of the ring sulphur, as suggested for the metalation of thiophene.⁹⁷



An excess of ethyl bromide was added to the remaining 2/3 of the reaction mixture in order to trap possible ring-opening products. After hydrolysis it was shown that about 15 components were present (vpc), of which the most abundant was the starting material (~ 60 %). The second most abundant component (~ 20 %) had a mass number of 168. The fragmentation pattern showed an easy loss of an ethyl group (29) to m/e 139, which was the base peak. This could be taken as evidence for 2-n-propyl-3,4,5-trimethylthiophene, which has a molecular weight of 168. However, the molecular ion fragment (m/e 168) was only 7 rel %, which seemed to be too low for a thiophene derivative (cf. Ref. 98 where the molecular fragments were more than about 22 rel % for most unbranched alkylthiophenes). Moreover, the M-1 fragment was

too abundant (12 rel %) for an n-propylthiophene derivative; both 2-n-propylthiophene and 5-methyl-2-n-propylthiophene had M-1 ions less abundant than 2 rel %.⁹⁸

From the ir spectrum of the crude product it was evident that ring-opening had occurred, leading to at least a terminal acetylene (3280, 2100, 2080 and 2160 cm^{-1}). The ^1H nmr spectrum was of little help since one of the methyl signals of the starting material appeared in the region where a nonconjugated acetylenic proton was expected to absorb⁹⁹ ($\delta = 1.8\text{--}2.1$ ppm). It should be mentioned that no signs could be found of the signals from the central methylene hydrogens of an n-propyl group, which are rather characteristic.¹⁰⁰ The structure of the compound with mass number 168 may have the structure 115, but 2-n-propyl-3,4,5-trimethylthiophene could not definitely be excluded.

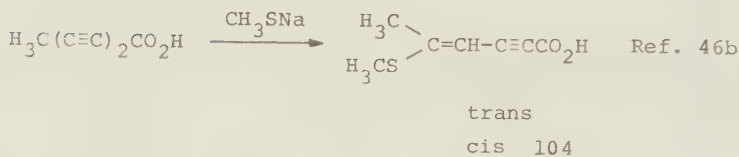
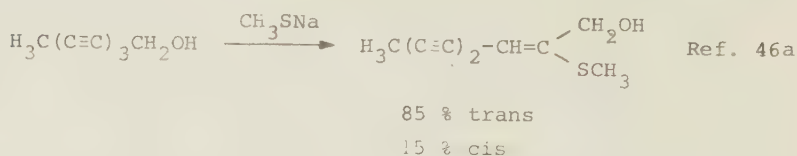


In any case, the above experiment demonstrated that side-chain lithiated thiophenes could undergo ring-opening, the route of which might be similar to that outlined by Gaertner.¹⁰

2.7 The addition of ethylmercaptan to some diacetylenes

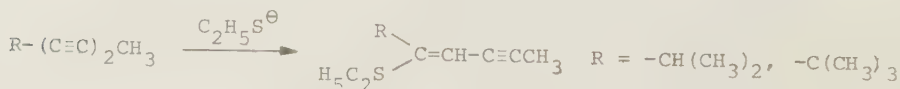
The addition of various nucleophiles to monoacetylenic compounds has been extensively studied by Truce et al.,⁴⁵ who found that trans addition was dominant. In contrast, the base-induced addition of alkylmercaptans to disubstituted diacetylenes or polyynes has been only rarely studied. As mentioned previously Bohlmann et al.^{43,46} used the above possibility to synthesize natural products. In some cases, one of the substituents on the diyne backbone was of polar nature, such as carboxyl^{46b} and hydroxymethyl.^{46a} In the presence of such groups the trans stereospecificity of the addition was lost, giving mixtures of Z- and E-thioenynes. However, the position selectivity was good and determined by the electronic properties of the substituents:

the nucleophile was directed to the most electron deficient terminal carbon of the triple bond array.

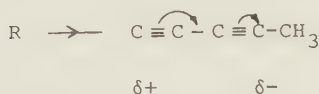


It should be mentioned that an attempt to prepare 104 by the ring-opening of 3-bromo-5-methyl-2-thiophenecarboxylic acid (125) with two equivalents of ethyllithium at +21°C failed. A mixture of components was formed but no acetylenes were detected (ir).

Petrov et al.^{44a} and Shostakovskii et al.^{44b} have also examined the addition of various reagents to diacetylenes. It was found that the thiolate groups were almost exclusively attached to the terminal unsubstituted carbon of monosubstituted conjugated diacetylenes. In the case of symmetrically disubstituted conjugated diacetylenes the attack of ethylthiolate took place on one of the identical terminal carbons of the diyne moiety.^{44a,b} Thus, 2-ethylthio-2-hexen-4-yne (9) and 3-ethylthio-3-octen-5-yne were formed from 2,4-hexadiyne and 3,5-octadiyne, respectively. The stereochemistry was not discussed. It was also claimed by Petrov et al.^{44a} that ethylthiolate added to the acetylenic carbon bearing the methyl group of 6-methyl-2,4-heptadiyne and 6,6-dimethyl-2,4-heptadiyne (108) to give 3-ethylthio-2-methyl-3-hepten-5-yne and 3-ethylthio-2,2-dimethyl-3-hepten-5-yne (30), respectively.

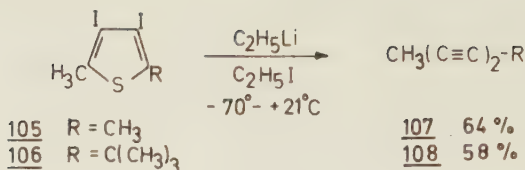


These results were explained by the propagation of the stronger +I effect of the branched alkyl groups through the π -bond system, making the "methyl carbon" more electron-rich than the "isopropyl" or "t-butyl carbon".



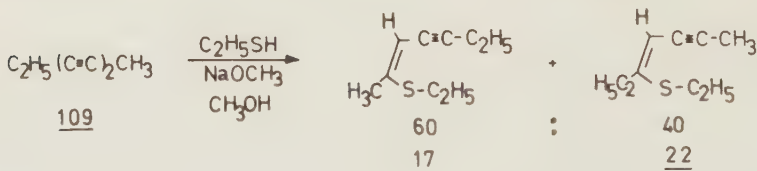
This explanation and also the results seemed somewhat far-fetched for steric reasons, and also due to the small difference in inductive forces between the alkyl groups. Disregarding sterical effects, one would guess that a mixture of positional isomers would be formed. Since both 30 and 26 were available from our ring-opening experiments (cf. 2.1) a direct comparison with the ir data published by Petrov et al.^{44a} revealed that 26 was identical with the substance found by these authors. Their experiment was repeated and it was shown by careful vpc analysis that 26 was formed exclusively and in a 65 % yield. Obviously an erroneous structure was suggested by the Russian workers,^{44a} who based their structure suggestion on the coupling constant between the methyl protons of the methyl group at the multiple bonds and the ethylenic proton. The splitting of the methyl signal was reported to be weak, which led these authors to the conclusion that the methyl group was situated at the triple bond. In this context a coupling constant of 1.5 Hz was regarded as small. It appeared in the present work that the coupling constant of the ethylenic methyl protons and the ethylenic proton of 26 was 1.4 Hz (the allylic coupling) and that of the acetylenic methyl protons and the ethylenic proton of 30 was 2.4 Hz (the propargylic coupling). The ring-opening reaction may accordingly become of some value when the sterically most unfavorable of two possible isomers of conjugated thioenynes is desired.

The diyne 108 was prepared in 58 % yield by treating 2-t-butyl-3,4-diiodo-5-methylthiophene (106) with two equivalents of ethereal ethyllithium and ethyl iodide. When the same reagents were applied on 3,4-diiodo-2,5-dimethylthiophene⁵² a 54 % yield of 2,4-hexadiyne (107) was obtained.



These examples of "double" ring-opening were similar to that reported by Wittig and Rings,¹⁷ except that these authors used only one equivalent of butyllithium. It does not seem likely that the "double" ring-opening of the 3,4-diiodo heterocycles proceeds through the 3,4-dilithiated ones as suggested by Wittig and Rings¹⁷ since as much as 70 % of diphenylbutadiyne was obtained in their experiment with one equivalent of butyllithium (20 % of the starting material was recovered). In theory only 50 % of the ring-opening could occur from the dilithiated diphenylthiophene.

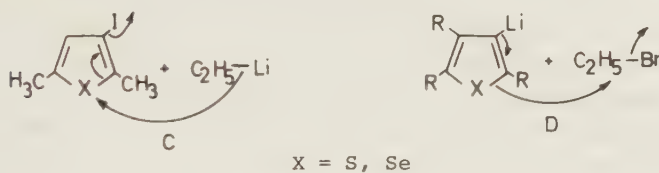
In order to test the hypothesis that disubstituted diacetylenes with electronically and sterically similar substituents would add ethylthiolate so as to give mixtures of isomers ethylthiolate was added to 2,4-heptadiyne (109) (see 3.4) according to the process described by Petrov et al.^{44a} It was indeed found, by comparison with authentic materials through vpc analysis, that 17 and 22 were formed in the ratio 60:40 (yield 52 % after removal of the starting material). Consequently the



ring-opening reactions may prove to be synthetically useful even in cases where the pure isomers are desired. The route via the ring-opening of suitable thiophene derivatives thus corresponds to regiospecific addition of thiolates to unsymmetrical diacetylenes.

2.8.1 Kinetics and discussion of the reaction mechanism

The very fast cleavage of the selenophene ring when 3-iodo-2,5-dimethylselenophene (1) was treated with ethyllithium at -70°C (see 2.1) made it at first doubtful that the 3-selenienyllithium derivative was an intermediate at all. The ethyllithium could possibly attack the selenium atom in a nucleophilic way with ring-cleavage as a result, as shown below (C). The enyne selenoether should in this case be formed more or less concertedly and therefore it would be impossible to trap any enyne selenolate with electrophiles. This reasoning could also be extended to the sulphur analogues.



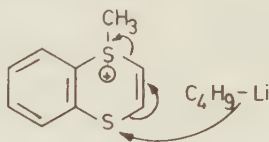
However, some experiments were performed that clearly rejected this mechanism.

1) The ring-opening also occurred when phenyllithium was used as a metal-introducing agent (cf. 2.1), but no phenyl-seleno enyne ether was detected.⁸ In the thiophene case, the enyne thiolate was trapped with dimethylsulphate, ethyl bromoacetate and benzyl bromide giving the corresponding thioethers 11a, b, and c⁵⁹ (see 2.1).

2) By lowering the reaction temperature to -110°C it was possible to isolate 2,5-dimethyl-3-selenophenecarboxylic acid⁸ (see 2.1).

These experiments showed that the selenium (or sulphur) atom was not necessarily attacked for the ring-opening to take place, and also that the 2,5-dimethyl-3-selenienyllithium almost certainly was an intermediate. A mechanism suggested by Jacobsen³⁰ (D) was also ruled out by these experiments. This mechanism involved an attack of the alkyl halide on the sulphur atom of the 3-thienyllithium derivatives. Nevertheless, the presence of an alkyl halide might influence the rate of the ring-opening. Nor could the selenium (or sulphur) atom of the aromatic rings be quaternized by alkyl halides followed by

halogen-metal exchange. Parham and Stright¹⁰² suggested that the ring-opening of benzo-1,4-dithiadiene could proceed as indicated below when this substance was treated with n-butyllithium followed by dimethylsulphate.



It was stated that almost no reaction took place between the sulphur heterocycle and butyllithium. Obviously the dimethyl sulphate reacted faster with benzo-1,4-dithiadiene than with butyllithium, which was unexpected.

Kinetic measurements of the ring-opening reaction of 2,5-dimethyl-3-thienyllithium, 2-t-butyl-5-methyl-3-thienyllithium, 5-t-butyl-2-methyl-3-thienyllithium, 5-methyl-2-phenyl-3-thienyllithium, 2-methyl-5-phenyl-3-thienyllithium and 2,5-dimethyl-4-phenyl-3-thienyllithium in ether were performed as follows. It was first demonstrated that the halogen-metal exchange between 3-iodo-2,5-dimethylthiophene (8), 3-iodo-5-methyl-2-phenylthiophene (59), 3-iodo-2-methyl-5-phenylthiophene (61) and 3-iodo-2,5-dimethyl-4-phenylthiophene (52) and phenyllithium was complete in less than 30 sec at -30°C for 8 and at $+20^{\circ}\text{C}$ for 52, 59, and 61. This was performed by quenching samples from the appropriate reaction mixtures with dimethylsulphate followed by vpc analysis. It was thus shown that the iodothiophenes were completely consumed in less than 30 sec and that iodobenzene and the corresponding 3-methylthiophene derivative (i.e. the trapped 3-thienyllithium derivative) were formed in about equal amounts. It was assumed that 2-t-butyl-3-iodo-5-methylthiophene (110) and 5-t-butyl-3-iodo-2-methylthiophene⁶¹ (29) behaved in the same way as 8, and therefore these substances were not checked. (The Wurtz-Fittig reaction in the case of 29 was prominent in the presence of alkyl halides (see 2.1), but with phenyllithium no alkyl halides were formed and the iodobenzene formed in the halogen-metal exchange was considered unreactive in Wurtz-Fittig couplings.)

By quenching samples from the reaction mixtures with

dimethylsulphate as mentioned above, the ring-opening reactions could be followed (vpc). It appeared that while the peak originating from the 3-methylthiophene derivatives decreased (in area), that originating from the corresponding methylthio enynes increased. In all cases but one the only by-products were the dehalogenated heterocycles amounting to less than 10 %. The exception was 2-methyl-5-phenyl-3-thienyllithium in which case several by-products were formed amounting to about 15 %, besides 10 % of the dehalogenated heterocycle. Accordingly the rate constant to be measured in this case probably would not reflect the ring-opening rate with acceptable accuracy. In the other cases, it was assumed with some justice that the thienyllithium derivatives reacted in only one way, namely to give the lithium enyne thiolates. The reactions could be followed until the peak of the 3-methylthiophene derivatives vanished (< 0.1 rel %), which means that if there were an equilibrium between the 3-thienyllithium derivatives and the corresponding lithium enyne thiolates, the equilibrium constants must be larger than 1000 in favour of the latter species. Thus the ΔG for the reaction was probably larger than 15 kJ/mol. In sum, the preliminary experiments described here demonstrated 1) that the halogen-metal exchanges were rapid and probably would not interfere with the ring-opening reactions; 2) that the ring-openings went to completeness, i.e. there existed no observable equilibrium between the thienyllithium derivatives and the corresponding lithium enyne thiolates; and 3) that there probably did not exist competing reactions, except in the case of 2-methyl-5-phenyl-3-thienyllithium. The formation of the dehalogenated heterocycles could be due to some proton source introduced in handling the samples to be quenched. This problem would possibly be eliminated in the kinetic experiments, in which the reaction mixtures were sealed in nmr tubes.

By using the nmr technique and simply integrating over the increasing signal belonging to the vinylic proton of the enyne thiolates, it was possible to determine the apparent reaction order with respect to these species. The reaction should be of the same order with respect to the corresponding 3-thienyllithium derivatives which seemed justified according to the preceding discussion.

The ring-opening of 4-phenyl-2,5-dimethyl-3-thienyllithium could not be followed by nmr due to the absence of vinylic protons. However, the preliminary quenching experiments indicated that this reaction was slower than that of 2-phenyl-5-methyl-3-thienyllithium (see exp. part).

Although there is no data available about the aggregate form of 3-thienyllithium derivatives (in ether), it was assumed that there exists an equilibrium between solvated dimers and monomers similar to the situation suggested for phenyllithium.¹⁰³⁻¹⁰⁵ Several kinetic models could then be set up by combining dimer and monomer reactions with the ring-opening reaction, as will be discussed below.

I. Let us look at the following model in which only the monomeric thienyllithium ring-opens and where A = 3-thienyllithium derivative and B = lithium enyne thiolate:



I.1. If $k_1 < k_{-1}$ and $k_2 \ll k_1$, k_{-1} one arrives at a rate expression that contains a square root:

$$K = \frac{k_1}{k_{-1}} = \frac{[A]^2}{[A_2]}, \quad 2[A_2] = C_B - [B] \Rightarrow$$

$$\Rightarrow \frac{d[B]}{dt} = k_2[A] = k_2 \sqrt{\frac{K}{2}} \sqrt{C_B - [B]} \Rightarrow \sqrt{C_B - [B]} = \sqrt{C_B} - \frac{k_2}{2} \sqrt{\frac{K}{2}} \cdot t$$

where C_B = total conc of B = $2 C_{A_2}$ (C_{A_2} = total conc of A_2)

$[A_2]$ = conc of species A_2 at different times

$[A]$ = conc of species A at different times

$[B]$ = conc of species B at different times

k_n = rate constants

This model implies that the order of the reaction in the enyne thiolate is 0.5.

I.2. By maintaining the relation $k_2 \ll k_1, k_{-1}$ but allowing $k_1 > k_{-1}$, a rate law is obtained which is of reaction order 1 with respect to the enyne thiolate:

$$[A] = C_B - [B] \Rightarrow \frac{dB}{dt} = k_2[A] = k_2 \cdot (C_B - [B]) \Rightarrow$$

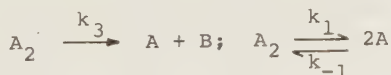
$$\Rightarrow -\ln C_B - [B] = -\ln C_B + k_2 \cdot t$$

I.3. Another situation arises if $k_{-1}, k_1 \ll k_2$. Then the equilibrium concentrations between the dimer and the monomer can not be maintained during the reaction. Therefore it is not permissible to use the equilibrium expression $K = \frac{[A]^2}{[A_2]}$ in the calculation of the rate expression which appeared to be of first order with respect to the enyne thiolate (steady-state approximation). In this case, however, the observed rate constant will be k_1 :

$$2[A_2] = C_B - [B] \Rightarrow \frac{d[B]}{dt} \approx -2 \frac{d[A_2]}{dt} = 2 k_1[A_2] = k_1(C_B - [B]) \Rightarrow$$

$$\Rightarrow -\ln(C_B - [B]) = -\ln C_B + k_1 \cdot t$$

II. A quite different model must be considered if only the dimeric thienyllithium derivatives can ring-open or ring-open much faster than the monomeric species:



II.1. If $k_1 < k_{-1}$ and $k_1, k_{-1} \gg k_3$, a first-order expression with respect to the enyne thiolate is obtained:

$$2[A_2] = (C_B - [B]) \Rightarrow \frac{d[B]}{dt} = k_3[A_2] = \frac{k_3}{2} (C_B - [B]) \Rightarrow$$

$$-\ln(C_B - [B]) = -\ln C_B + \frac{k_3}{2} t$$

II.2. If $k_1, k_{-1} \gg k_3$, but $k_1 > k_{-1}$, a second-order rate law emerges:

$$K = \frac{[A]^2}{[A_2]}, \quad C_B = [A] + [B] \Rightarrow \frac{d[B]}{dt} = k_3[A_2] = \frac{k_3}{K} (C_B - [B])^2 \Rightarrow$$

$$(C_B - [B])^{-1} = C_B^{-1} + \frac{k_3}{K} \cdot t$$

III. It is also possible that the dimer is converted to two molecules of the ring-opened product in a concerted way:



III.1. If $k_1, k_{-1} \gg k_4$ and $k_1 < k_{-1}$, the rate equation for the formation of B will become a first-order expression:

$$2[A_2] = (C_B - [B]) \Rightarrow \frac{d[B]}{dt} = 2k_4[A_2] = k_4 (C_B - [B]) \Rightarrow$$

$$-\ln (C_B - [B]) = -\ln C_B + k_4 \cdot t$$

III.2. A second-order rate law is obtained if $k_1 > k_{-1}$ and $k_1, k_{-1} \gg k_4$:

$$K = \frac{[A]^2}{[A_2]}, \quad [A] = C_B - [B] \Rightarrow \frac{d[B]}{dt} = 2k_4[A_2] = \frac{2k_4}{K} (C_B - [B])^2 \Rightarrow$$

$$(C_B - [B])^{-1} = C_B^{-1} + \frac{2k_4}{K} \cdot t$$

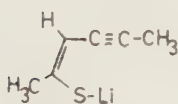
These models should be regarded as a first approximation of the kinetic situation of the ring-opening reaction.

The experimental data were only consistent (within the limits of error; see exp. part) with first-order rate laws with respect to the enyne thiolates B (Table 1). Consequently, models I.1, II.2, and III.2 could be rejected. Four models then remained, all of which were of first order with respect to the enyne thiolate, namely I.2, I.3, II.1, and III.1. It is however difficult to distinguish between these, and it is possible that both monomers and dimers of the 3-thienyllithium derivatives are reactive species, giving rise to fractional reaction orders close to unity. More refined methods than those used in the present work, must be employed if such kinetic detail is to be revealed.

It was somewhat unexpected to find that 2-t-butyl-5-methyl-3-thienyllithium ring-opened at a slower rate than

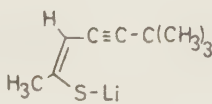
2,5-dimethyl-3-thienyllithium (Table 1). If the +I effect was of any importance, the expected result would be in the opposite direction (see 2.2). However, in a "dimeric" transition state,* the t-butyl groups could possibly exhibit some steric hindrance toward the ring-opening. Naturally, the same reasoning could be applied to other large groups in the 2-position, e.g. phenyl, and thus the influence of the inductive effects could be completely overshadowed. The rate differences are rather small and the above explanation for the observed differences should be regarded as a mere suggestion. Moreover, the situation may be very complicated if the ring-opening reactions proceed via different mechanisms in different cases.

Table 1. Pseudo first order rate constants, $k \times 10^3$ (min^{-1}), for the formation of some lithium enyne thiolates (E-I) at -0.5°C in ether from the corresponding 3-thienyllithium derivatives. Least-squares treatment (correlation coefficients > 0.99 in all cases).



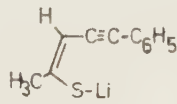
E

104±1



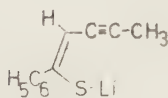
F

36.9±0.6



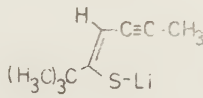
G

13.7±0.2



H

3.22±0.07

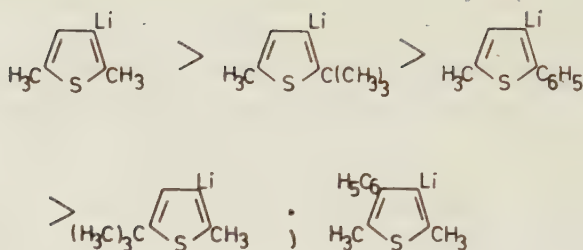


I

1.24±0.03

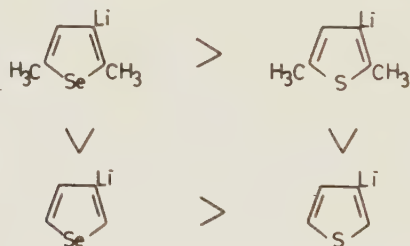
On the basis of the rate constants, the following order of reactivity may be established:

* e.g. model II.1 (cf. Ref. 101b).



Since by-product formation was extensive in the case of 2-methyl-5-phenyl-3-thienyllithium, this compound is omitted (see p 53).

Other experiments (see 2.1 and 2.2) indicated that 2,5-dimethyl-3-thienyllithium was more reactive than 3-thienyllithium. The same was true for the corresponding selenophene analogues, and the selenophene compounds were more reactive than their sulphur counterparts.



The activation parameters for the ring-opening of 2,5-dimethyl-3-thienyllithium in diethylether were obtained by measuring the pseudo first-order reaction rate constants at five different temperatures (-29.0, -18.0, -17.0, -8.5, -0.5°C) and then applying the Eyring equation¹⁰⁶ ($\ln \frac{k}{T}$ was plotted against $\frac{1}{T}$):

$$\ln \frac{k}{T} = - \frac{\Delta H^*}{R} \cdot \frac{1}{T} + \frac{\Delta S^*}{R} + \ln \frac{\kappa \cdot K}{h}$$

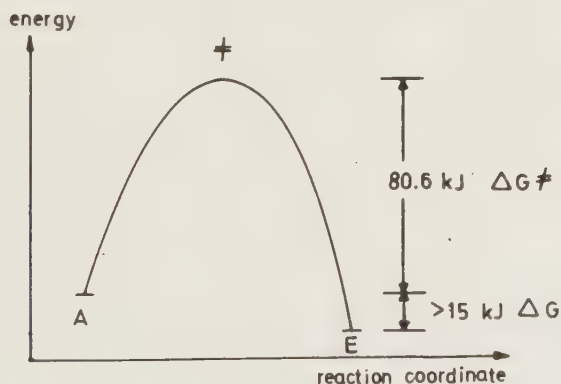
k = first-order rate constant; T = temperature °K; ΔH^* = activation enthalpy; R = the gas constant 8.31434 J/mol.deg; ΔS^* = activation entropy; κ = the transmission coefficient = 1; K = Boltzmann's constant = 1.381×10^{-16} erg deg⁻¹ molecule⁻¹; h = Planck's constant = 1.104×10^{-28} erg min.

The results are presented in Table 2.

Table 2. Rate constants and activation parameters for the ring-opening of 2,5-dimethyl-3-thienyllithium. Least-squares treatment (correlation coefficients > 0.99 in all cases).

Temp. °K (°C)	$k \times 10^{-3}$ (min ⁻¹)	$\Delta H^\ddagger$ (kJ/mol)	$\Delta S^\ddagger$ (J/mol.deg)	$\Delta G^\ddagger$ (kJ/mol)
272.7 (-0.5)	104±1	66.4±3.7	-52±14	80.6±7.5
264.7 (-8.5)	57.3±0.8			
256.2 (-17.0)	16.5±0.2			
255.2 (-18.0)	13.6±0.3			
244.2 (-29.0)	3.5±0.1			

Obviously the enthalpy of activation is the main factor determining the free energy of activation at ordinary temperatures. The negative value of the entropy of activation indicates a more ordered transition state than ground state. The energy profile for the ring-opening of 2,5-dimethyl-3-thienyllithium may be represented as shown in the diagram below.



It should be emphasized, that if the determined rate constants include the monomer-dimer equilibrium (k_1 , model I.3) nothing could be said at present about the reactivity order or the activation parameters of the ring-opening reaction. The

kinetic results obtained in this work should be regarded as preliminary ones.

In some cases it seemed probable that the ring-opening rate was slowed down by the precipitation of the 3-thienyllithium derivatives. This became evident when 2,5-dimethyl-3-thienyllithium was prepared in hexane, where the thienyllithium precipitated. The ring-opening was followed by vpc after the quenching of samples from the reaction mixture with dimethylsulphate. While the cleavage was complete in less than 10 minutes in ether (a homogeneous system) it took more than 30 minutes in hexane (a heterogeneous system).

As previously mentioned, the ring-cleavage reactions could be regarded as 1,2-eliminations, and the similarity to ElcB eliminations¹⁰⁷ is obvious. However, there is no evidence as to whether the reaction is heterolytic or homolytic. Thus the process may be represented in two ways:

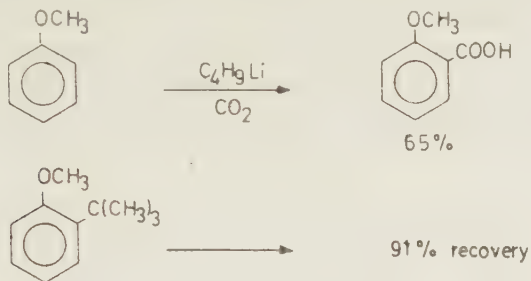


It should just be mentioned that CIDNP¹⁰⁸ (chemically induced dynamic nuclear polarization) phenomena have not been observed.

2.8.2 The role of non-bonded electrons

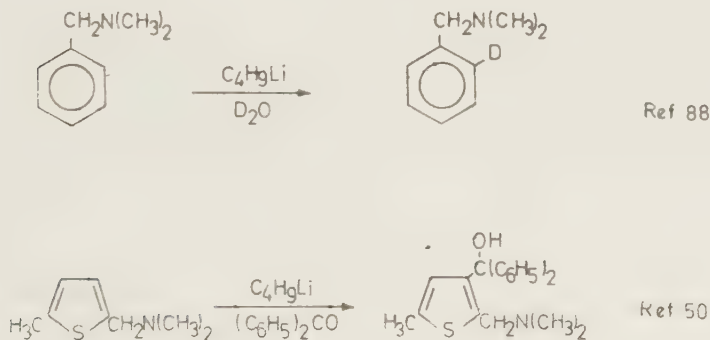
It has been shown that aromatic nuclei bearing certain substituents with non-bonded electrons were selectively metalated by e.g. butyllithium in the positions ortho to these substituents ($-\text{OCH}_3$,^{48,87} $-\text{CH}_2-\text{N}(\text{CH}_3)_2$,^{50,88} and $\text{SO}_2\text{N}(\text{CH}_3)_2$).^{49,89} These groups not only directed the metalation but also enhanced it since e.g. benzene was not metalated by butyllithium while anisole was⁸⁷ (at least to 65 % and selectively in the ortho position). It was originally proposed by Roberts and Curtin⁸⁷ that butyllithium formed a complex with the free electron pairs on oxygen in anisole. Such a complex should also increase the -I effect of the methoxy group making the ortho hydrogen more labile. In a recent work, Slocum et al.⁹⁰ showed that when

the complexation ability of the methoxy group was restricted by a t-butyl group, metalation was very much suppressed:



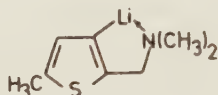
When tetramethylethylenediamine (TMEDA) was added metalation took place only to about 25 %, but in the position ortho to the methoxy group. These results indicated that the complexation of the metalating agent with the free electron pair on oxygen was more effective to bring about metalation than the inductive force of the methoxy group. The same type of argument seems to hold for the dimethylaminomethyl group, the inductive effect of which should be quite small (cf. $-\text{CH}_2\text{OCH}_3$ $\sigma^- = 0.031$ ⁹¹). It should only be the complexation that makes metalation possible in such cases.

The situations in the methoxy and dimethylamino cases

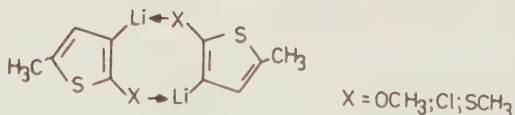


Scheme 9

should be different once the lithium atom is in position. It seemed reasonable to assume that the complexation effect was still operative in the dimethylaminomethyl case, since a five-membered complex could be drawn, while a four-membered complex which must be considered for the methoxy case seemed less favorable. The ring-opening tendency of the methoxy and chloro com-



pounds should reflect the situation in which the lithium atom was already incorporated in the molecule. The facts that 2-methoxy-5-methyl-3-thienyllithium and 2-chloro-5-methyl-3-thienyllithium were stable toward ring-opening, while 5-methoxy-2-methyl-3-thienyllithium and 5-chloro-2-methyl-3-thienyllithium were not, indicated that it was the -I effect of the methoxy and chloro substituents that was responsible for the resistance to ring-opening, and not the existence of "free" electrons. Still, the "free" electrons might be involved. It has been demonstrated that organolithium compounds were not monomers but dimers and larger clusters.⁹² An increase in stability of the 3-thienyllithium derivatives by clustering must accordingly be considered. Since only the "ortho" compounds were stable (i.e. where the methoxy or chloro groups were ortho to lithium), and not the "meta" compounds, the cluster seemed to call for a certain geometry. One may suggest a kind of cyclic dimer with mutual stabilization for the ortho compound (see below), where the non-bonded electrons are donated to the electron-deficient lithium atom. For the meta

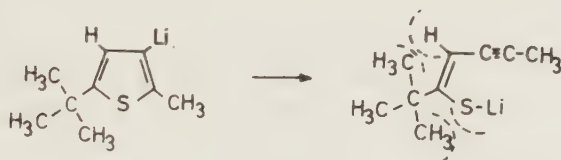


compounds, the mutuality can not be easily attained, which together with less inductive withdrawal of electrons from the anionic center makes these compounds more susceptible to ring-opening. The fact that 5-N,N-dimethylaminomethyl-2-methyl-3-thienyllithium ring-opened, but 2-N,N-dimethylaminomethyl-5-

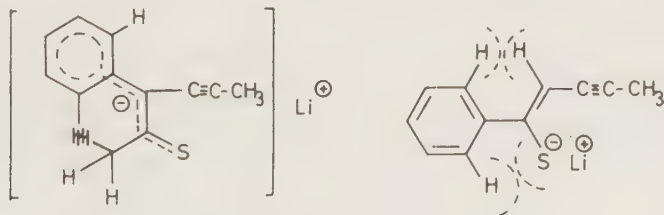
methyl-3-thienyllithium did not, indicated that an intramolecular chelate (ortho case) was more effective in stabilizing the lithium derivatives than a possible intermolecular one ("meta" case). It could also be concluded that the participation of the non-bonded electrons of nitrogen was enough to prevent ring-opening where no substantial inductive forces could be involved.

2.8.3 The role of steric crowding

It was found in the kinetic measurements that 5-*t*-butyl-2-methyl-3-thienyllithium ring-opened slower than 2,5-dimethyl-3-thienyllithium by a factor of 83. Disregarding the dimer-monomer equilibrium of the thienyllithium derivatives, it seems tempting to explain this result with a kind of "back-strain", exerted by the close approach of the *t*-butyl group, the "4-proton" and the sulphur atom as the reaction proceeds. Similar arguments can be



put forward in the case of 2,5-dimethyl-4-phenyl-3-thienyllithium and 2-methyl-5-phenyl-3-thienyllithium as well (left and right below), if planar arrangements are assumed. (It has been shown that atropisomerism arises in crowded styrenes.¹⁸⁷) The



slow ring-opening of the latter species is however uncertain as previously mentioned (see 2.8.1). In the former case there seems to exist the possibility for conjugation between the benzene

ring and the anionic center at the sulphur atom. This could increase the steric interaction between the ortho protons of the benzene ring and the protons of the vinylic methyl group. There also seems to be a possibility for rotation around the ethylenic bond, but this was not examined.

2.9 Mass spectra

There were two main purposes for recording mass spectra in this work, namely to find out the molecular weight of a compound and to distinguish between alkylthiophenes and their isomeric vinylacetylenic thioethers. Since mass spectral data for vinylacetylenic thioethers and selenoethers became available some of these isologous compounds could be compared with respect to their fragmentation patterns.

One should not attach too much importance to the relative intensities of the fragments since the spectra were recorded during a 5 year period of time and no deliberate precautions were made to equalize the recording conditions. Comparisons were only made when the combined vpc-mass spectrometer equipment was used, which of course introduced additional error, especially concerning the heat sensitive acetylenic compounds. Nevertheless, some general reproducible features were distinguished (Table 3).

The molecular ion fragment was the base peak for most of the enyne thioethers (and selenoethers). Exceptions to this rule were found for (Z)-1-ethylseleno-1-methylthio-1-penten-3-yne (93) (base peak at M-109) and (Z)-3-ethylthio-3-nonen-5-yne (23) (base peak at M-57). In the latter case, the molecular ion represented 89 rel %, which was not in agreement with the fragmentation of n-propylthiophenes or ethylthiophenes. These substances should give base peaks at M-29 and M-15, respectively.⁹⁸ It is well known that most simple alkylthiophenes give a base peak due to "β-cleavage",¹¹⁰ with a molecular ion of relatively low abundance (20-40 %). Accordingly it was in some cases no



problem to decide which compound was an alkylthiophene or an enyne thioether.

Quite abundant fragments of the ethylthio enynes were those originating from the RCX ion ($R = CH_3, H$) and from the loss of XC_2H_5 . The CH_3CX fragment was especially conspicuous for enynes with the atomic arrangement shown below.



The loss of XC_2H_5 was more important when $X = Se$ than when $X = S$, indicating the weaker carbon-selenium bond than carbon-sulphur bond. The above-mentioned fragmentations were almost negligible for the alkylthiophenes. The fragment at m/e 91 ($C_7H_7^+$, tropylium) was prominent for enyne thioethers (and selenoethers) with seven-carbon chains while this was not so in the cases of the isomeric thiophenes.

Selenium has a characteristic isotopic pattern which made it easy to decide which of the fragments contained this atom. For example, both (Z)-2-ethylseleno-2-hepten-4-yne (14) and (Z)-3-ethylseleno-3-hepten-5-yne (15) (m.wt. 202, ^{80}Se) had a quite abundant fragment at m/e 93 (67 resp 29 %). This could be due to the $(M-SeC_2H_5)^+$ or the $CHSe^+$ ions. Since the fragment did not contain selenium it had to be the $(M-SeC_2H_5)^+$ ion. The presence of selenium atoms as well as of chlorine atoms in the molecule, was also of importance in obtaining a piece of evidence for the structure of 72. As shown in Fig. 1 the calculated mass distribution of $C_8H_2Se_2Cl_4$ is almost identical with that experimentally found for 72. In order to trace the molecular ion fragment it was necessary to use the direct inlet system of the mass spectrometer due to the lability of the substance.

The mass spectra of the phenyl substituted compounds were too similar to be of any help in distinguishing between the phenyl thiophenes and the isomeric phenyl substituted vinyl-acetylenic thioethers.

Table 3. Some selected fragments in the mass spectra of some vinyl acetylenic thio- and selenoethers and some of their heterocyclic isomers. The numbers in the table represent percent values of the base peak.

Substance	M	M-15	C ₂ H ₂	C ₂ H ₅	C ₃ H ₇	C ₄ H ₆	C ₄ H ₉	SC ₂ H ₅	C ₅ H ₇	C ₅ H ₉	SC ₂ H ₅	SCCH ₃	SCCH ₃	C ₇ H ₇	SCCH ₃	SCCH ₃	C ₃ H ₃
(Z)-1-ethylthio-1-buten-3-yne (43)	100	61	26			65				100 ^a							68
(Z)-1-ethylseleno-1-buten-3-yne (47)	100	26	50														22
Ethylthiophene (44)	41	100	4		4				26								71
(Z)-2-ethylthio-2-hexen-4-yne (9)	100	34	23	13				11							53		11
(Z)-2-ethylseleno-2-hexen-4-yne (5)	100	9	15	10						19							9
(Z)-2-ethylthio-2-hepten-4-yne (17)	100	19	19	28	12	12	12	12	27					31	77		26
(Z)-2-ethylseleno-2-hepten-4-yne (14)	100	8	13	23	8												17
(Z)-3-ethylthio-3-hepten-5-yne (22)	100	25	17	21	12	8			29					54	13		25
(Z)-3-ethylseleno-3-hepten-5-yne (15)	100	5	9	15	5									100			18
(Z)-2-ethylthio-6-methyl-2-octen-4-yne (18)	100	12	76	12	47												35
(Z)-3-ethylthio-3-nonen-5-yne (23)	89	15	44	7	100								41 ^b				26

Table 3. (Cont.)

Substance	M	M-15	M-28	M-29	M-43	M-54	M-57	M-61	M-67	M-77	M-109	107	93	91	59	45	39
2-ethyl-5-n-propylthiophene (24)	30	12		100	4		7			4				10	3	8	7
2-s-butyl-5-ethylthiophene (20)	20	6		100			7			3				7	9	9	9
(Z)-2-ethylthio-5-methylthio-2-penten-4-yne (81)	100	56		3	19			13						6	81	88	19
(Z)-2-ethyl-seleno-5-methylthio-2-penten-4-yne (86)	100	25	11	3	19			16		56		16		17	8	47	42
(Z)-1-ethylthio-1-methylthio-1-penten-3-yne (89)	100	15	4	8	6			17						28	14	48	39
(Z)-1-ethyl-seleno-1-methylthio-1-penten-3-yne (93)	72	1		4	3					100			18	4	9	37	21
3-ethyl-5-methyl-2-methylthiothiophene (82)	83	100	3	3	6			11						6	14	18	11
(Z)-2-ethylthio-2-penten-4-yne (84)	80	25		38			10	10	100 ^c					100 ^c	23		24
(Z)-2-ethyl-seleno-2-penten-4-yne (87)	100	20		78			14		28	86		28	25	19		59	81

Table 3. (Cont.)

Substance	M	C_3H_3	C_2H_2	C_2H_5	C_3H_4	C_4H_6	C_4H_9	SC_2H_5	SC_2H_5	SCCH_3	C_5H_9	C_5H_7	C_5H_5	SC_2H_5	SCCH_3	C_5H_9	C_4H_7	SCCH_3	SC_2H_5	C_3H_3
(Z)-2-ethylthio-3,6-dimethyl-2-hepten-4-yne (26)	100	14	6					54				86					30	32	12	18
(Z)-3-ethylthio-2,2-dimethyl-3-hepten-5-yne (30)	100	58	6					11				21					16	62	7	14
5-t-butyl-3-ethyl-2-methylthiophene (31)	18	100	10					1				2					4	2	5	5
2-t-butyl-3-ethyl-5-methylthiophene (28)	16	100	1									1					2	4	2	3
(Z)-2-ethylthio-1-phenyl-2-penten-4-yne (51)	100	89	18															31	19	7
(Z)-2-ethylthio-1-phenyl-1-penten-3-yne (58)	100	27	17															6	10	4
3-ethyl-5-methyl-2-phenylthiophene (50)	98	100	24															17	6	6
(Z)-1-ethylthio-1-methylthio-1-hepten-3-yne (90)	100	6	55	12	27	3	30										45	12	39	18

^a the same fragment; ^b m/e = 73; ^c the same fragment.

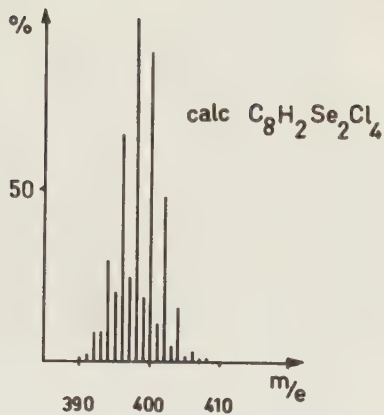
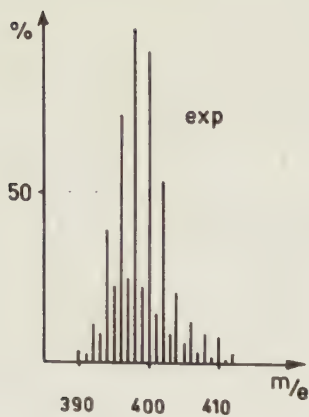


Fig. 1. Experimentally found mass distribution for the molecular ion of compound 72 (left) and the calculated mass distribution for $C_8H_2Se_2Cl_4$ (right). The peak at $m/e = 398$ is normalized to 100 %.

3. SYNTHESIS OF THE STARTING MATERIALS AND REFERENCE SUBSTANCES

Introduction

Since the chemistry of thiophene¹¹¹ and selenophene¹¹² has been reviewed, only some principles of preparation used in this work will be mentioned.

Electrophilic substitution. This type of reaction has been widely used in this work, e.g. halogenation and acetylation of the heterocycles and their derivatives.

Metalation and halogen-metal exchange. In order to prepare heterocyclic derivatives with substituents that can not be introduced by electrophilic substitution, metalation and halogen-metal exchange has frequently been applied. By action of appropriate polar substrates the heterocyclic lithium derivatives were converted to the desired compounds. Organolithium chemistry has been extensively reviewed.^{101a,113-115}

Cyclization has been used for the preparation of 2,5-dimethylfuran, 2,5-dimethylselenophene (111), selenophene (46), [8](2,5)-thiophenophane (38) and [11](2,5)-thiophenophane (39).

Side-chain reactions have been applied when the above reaction types did not lead directly to the desired materials.

3.1 Furan derivatives

2,5-Dimethyl-3-iodofuran (34) was prepared according to an existing procedure.

Through a Paal-Knorr synthesis, 2,5-dimethylfuran was formed from 2,4-hexanedione, acetic anhydride and zinc chloride.¹¹⁶ The dimethylfuran was mercurated with mercury(II) acetate to give 2,5-dimethyl-3-furylmercuryacetate together with some 2,5-dimethyl-3,4-difurylmercuryacetate. This mixture was iodinated with iodine and potassium iodide, yielding 3-iodo-2,5-dimethylfuran (34) and 3,4-diiodo-2,5-dimethylfuran.¹¹⁷ 3-Bromofuran¹¹⁸ was available in these laboratories.

3.2 Selenophene (46)

By heating sodium succinate with phosphorus triselenide

Foa¹¹⁹ believed to have synthesized selenophene (1909). This is a well known procedure for the preparation of thiophene when phosphorus trisulphide is used.¹²⁰ When Foa's experiment was repeated by Bogert and Andersen¹²¹ (1926), these authors were not able to reproduce Foa's result but had to relinquish further study on selenophene. One year later Mazza and Solazzo¹²² reported the preparation of what was believed to be selenophene by heating selenium in a current of acetylene. This result was confirmed by Briscoe et al.^{123,124} who, ostensibly were unaware of Mazza's and Solazzo's experiment, prepared selenophene in essentially the same way, i.e. by heating selenium in a current of acetylene in a Pyrex tube. Later Suginome et al.^{80a} and Chierici¹²⁵ et al. used this procedure. The yield was reported to be 30-40 % based on selenium.

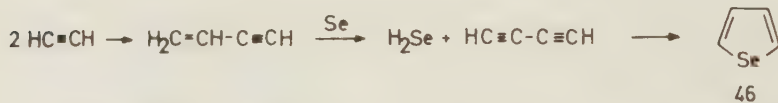
Yur'ev et al.¹²⁶ prepared selenophene from 1,3-butadiene and selenium dioxide with chromium(III)oxide:alumina as a catalyst at 450-550°C. The yield was around 10 %, which could be increased to 13 % with the use of a mixture of butenes and to 19 % if 1,3-butadiene was heated with selenium to 550°C, which was reported by Arbuzov et al.¹²⁷ It was also noted by Yur'ev¹²⁸ that furan together with hydrogen selenide at 550°C yielded selenophene.

A modification of the method of Mazza and Solazzo appeared in 1965 when Ried et al.¹²⁹ used alumina as a catalyst, which together with selenium and acetylene gave a 25 % yield of selenophene.

Since the highest yields (30-40 %) were obtained with the method of Mazza and Solazzo as reported by Suginome et al.^{80a} and Chienici et al.¹²⁵, it was quite naturally tried. However, these relatively good yields could not be reproduced. Besides the earlier reported formation of benzene, selenophene and several high boiling substances^{80b, 123-125} toluene was also formed. In order to separate toluene and selenophene it was necessary to use preparative gas chromatography since the boiling points are almost identical (110-111°C). The yield was estimated to be about 5 % of impure selenophene contaminated with 10-20 % of toluene after an ordinary distillation with an efficient column. At first it seemed unlikely that a seven-carbon hydrocarbon should be formed by heating acetylene. The

presence of acetone, despite the precautions of leading the acetylene through several wash bottles with water and conc. sulphuric acid, might be responsible for the odd-carbon unit. Therefore some experiments with acetone-free acetylene were performed. The toluene was still present in the reaction products.

Cullis and Franklin¹³⁰ made a detailed investigation of the pyrolysis of acetylene at temperatures ranging from 500 to 1000°C. They found that vinylacetylene was the sole initial reaction product which was probably dehydrogenated to diacetylene by carbonaceous reaction products. It was reported by Briscoe et al.,^{123,124} and by others,^{80a,125} that such materials increased the yield of selenophene when mixed with selenium. Moreover it was suggested that hydrogen selenide was formed in the reaction between selenium and acetylene.¹²³ Thus it seems reasonable to anticipate that selenophene originates from the addition of hydrogen selenide to diacetylene.



This parallels the way in which some thiophene derivatives have been prepared¹³¹ and the biogenesis of thiophene derivatives.⁴³

In the work of Cullis and Franklin,¹³⁰ it was also found that fragments with an odd number of carbon atoms were formed, e.g. methylacetylene and allene. The observation that toluene was present among the products in the selenophene synthesis might be explained by assuming the net reaction between two acetylene molecules and one three-carbon fragment.

Since the presence of toluene was a serious problem, the modification of adding alumina to the reaction tube (Pyrex) was tried according to Read et al.¹²⁹ In this way a 33 % yield of selenophene was obtained with only minor amounts of toluene (2 %) after one distillation of the crude product. It was also noticed that the amount of toluene was increased with an increase in the reaction temperature. The best result was obtained at 340-360°C. Also the reaction time was affected by the use of alumina. After two hours the reaction subsided (no more

pyrolysate was formed) with the catalyst, while about 6 hours were needed without it. Umezawa^{80b} examined the composition of the higher boiling fraction of the selenophene synthesis and claimed that the major by-product, with m.p. 123-124.5°C, was selenolo[3,4-b]selenophene. The structure determination was mainly based on dipole moment measurements. However, by a combination of mass spectrometry, ¹³C nmr, ⁷⁷Se nmr and dipole moment measurements it was demonstrated by Gronowitz et al.¹⁸⁶ that the substance, obtained in the same way as Umezawa, in fact was selenolo[3,2-b]selenophene. A detailed reaction product analysis of the selenophene synthesis is in progress in these laboratories.

Since substantial amounts of selenophene were needed in this work, a special tube oven containing 10 tubes was constructed (Fig. 2), which delivered about 100 g selenophene per day under optimal conditions.

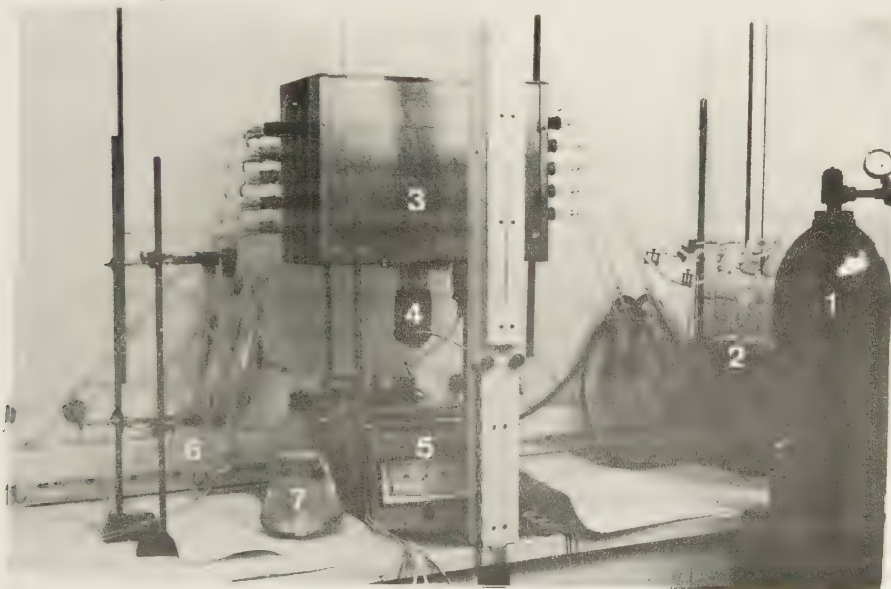


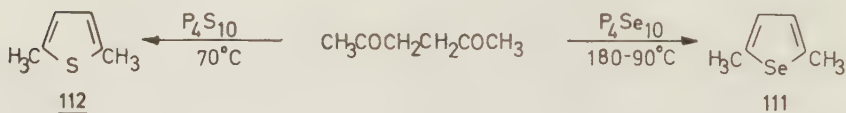
Fig. 2. Tube oven for the selenophene preparation. 1) Acetylene cylinder. 2) Wash bottles with paraffin oil for gas flow control. 3) Tube oven. The tubes are made of Pyrex glass and are placed in ceramic cylinders. 4) Fan motor. 5) Temperature control device. 6) Flasks for collection of the crude product. 7) E-flask with 2 N NaOH solution (for removal of H₂Se of the outlet gas stream).

Mack¹³² published an elegant method for preparing tellurophene by adding sodium telluride to diacetylene in methanol. By the use of sodium selenide, selenophene was obtained in a 60 % yield, as personally communicated to us by Brandsma and Meijer.¹³³ This method seems to be of greatest value when a smaller amount of selenophene is needed (in the range of 50-100 g) while the method described by Read et al.¹²⁹ and used in this work is convenient when a continuous production of selenophene is desirable.

3.3 Selenophene and thiophene derivatives

3.3.1 Substances related to 2,5-dimethyl-substituted heterocycles

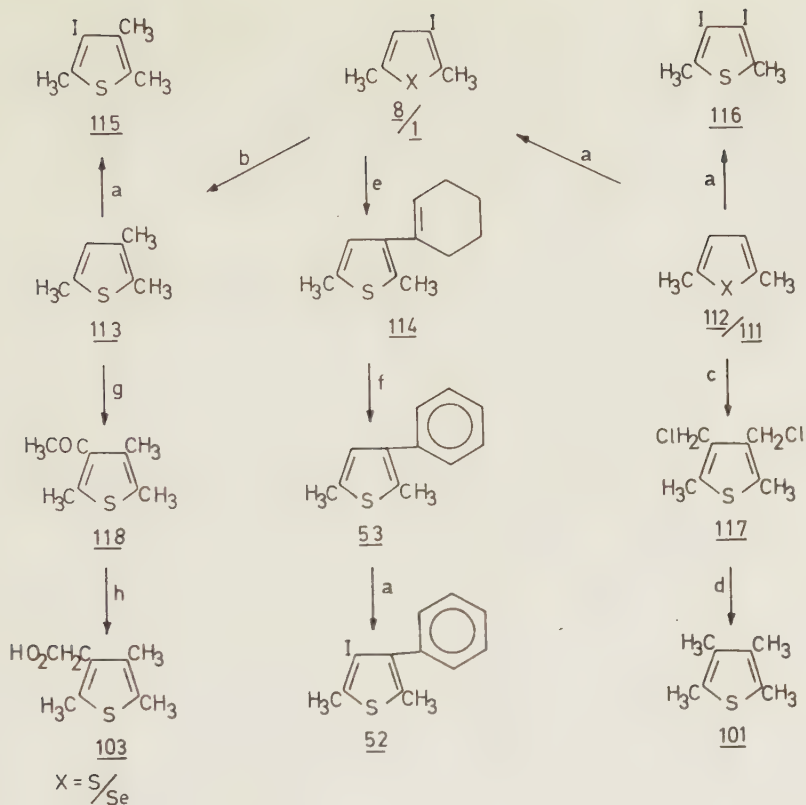
For the synthesis of 2,5-dimethylselenophene (111) the classical work by Paal¹³⁴ was followed, in which 2,4-hexanedione was heated with phosphorus pentaselenide. It should just



be mentioned that the conditions to bring about the reaction with the phosphorus pentaselenide (180-190°C, autoclave) are far more drastic than those with the sulphide^{135a} (spontaneous reaction in an open vessel at $\approx 70-80^\circ\text{C}$). Also the yield of 111 was much lower than that of 2,5-dimethylthiophene (112) (20 % resp 87 %).

The following discussion is represented in Scheme 10.

Iodination of 111 and 112 was accomplished with the iodine-iodic acid method introduced by Wirth et al.^{135b} Somewhat milder reaction conditions had to be used with 111¹ than with 112.⁵² At temperatures where 112 gave a good yield of 2,5-dimethyl-3-iodothiophene (8)⁵² only solid black masses remained from 111. At lower temperatures and with smaller amounts of the catalyst (concentrated sulphuric acid) 111 was easily converted to 2,5-dimethyl-3-iodoselenophene¹ (1) (74 %). By carrying out a metal-



- a) I_2 , HIO_3
 b) $n\text{-BuLi}$, -70°C , DMS
 c) HCl , trioxane
 d) LiAlH_4

- e) BuLi , cyclohexanone
 f) Chloranil
 g) Acetic anhydride, HClO_4
 h) TTN, MeOH

Scheme 10

halogen exchange between 8 and $n\text{-butyllithium}$ at -70°C , 2,5-dimethyl-3-thienyllithium⁵² was prepared and used as an intermediate for the synthesis of 2,3,5-trimethylthiophene¹³⁶ (113) and 2,5-dimethyl-3-(1-cyclohexenyl)thiophene¹³⁷ (114). The

former substance was obtained by alkylation of the 3-thienyl-lithium derivative with dimethylsulphate; the latter by the reaction with cyclohexanone as described by Gronowitz et al.¹³⁷ Subsequent aromatization of 114 with chloranil in chlorobenzene furnished 3-phenyl-2,5-dimethylthiophene^{137,138} (53), which was iodinated (by using the iodine-iodic acid method)^{135b} to give 4-iodo-3-phenyl-2,5-dimethylthiophene (52). The yield was 22 % based on 8.

The iodine-iodic acid method^{135b} was further used to prepare 3-iodo-2,4,5-trimethylthiophene (115) (from 113) and 3,4-diiodo-2,5-dimethylthiophene⁵² (116) (from 8).

In order to obtain tetramethylthiophene¹¹⁷ (101), 112 was chloromethylated with sym-trioxane and hydrogen chloride to yield 3,4-bischloromethyl-2,5-dimethylthiophene¹¹⁷ (117), which was subsequently reduced with lithium aluminum hydride in ether.

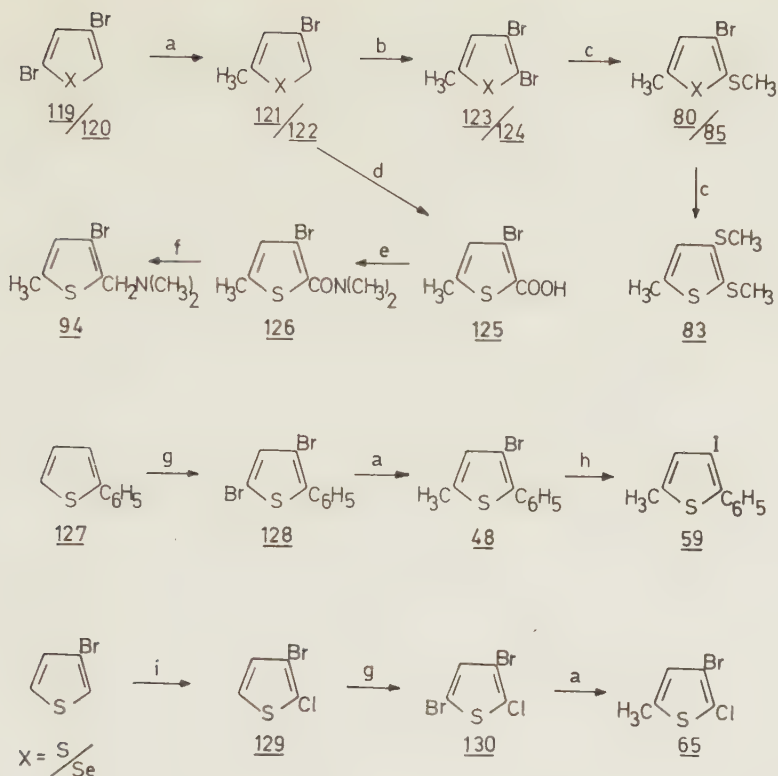
Acetylation of compound 113 at room temperature with acetic anhydride and perchloric acid¹³⁹ afforded 3-acetyl-2,4,5-trimethylthiophene (118) in 56 % yield. The acetyl derivative 118 was oxidized with thallium trinitrate trihydrate in methanol¹⁴⁰ to give methyl 2,4,5-trimethyl-3-thienylacetate, which after hydrolysis yielded the corresponding acetic acid 103.

The purpose of synthesizing substances 1, 8, 52, 115, and 116 was to use these compounds in ring-opening experiments in which the halogen atoms were to be replaced by lithium.

Compound 101 was to be used in metalation experiments as was compound 112 (see 2.6), and the acid 103 was used as a reference substance (see 2.6).

3.3.2 Substances related to 4-halo-2-methyl-substituted heterocycles

Two slightly different reaction paths were used to synthesize the compounds related to 4-halo-2-methyl-substituted heterocycles. In one of these paths, the β -halogen, i.e. bromine was already present at the start of the building-up of the side-chains (see Scheme 11). In the second path the halogen (bromine) was introduced at a later stage by brominating the appropriate heterocyclic compound (see Scheme 12).



- a) BuLi, DMS
 b) X = S, Br₂, HAc +25°C
 X = Se, Br₂, HAc/CS₂ -30°C
 c) BuLi, CH₃SSCH₃
 d) LiN(i-Pr)₂, CO₂, +25°C
 e) SOCl₂, HN(CH₃)₂
 f) LiAlH₄
 g) Br₂, HAc
 h) BuLi, I₂
 i) NCS, HAc

Scheme 11

Useful starting materials in the first case (Scheme 11) were 2,4-dibromothiophene¹⁴¹ (119) or -selenophene¹⁴² (120), which were converted to the 4-bromo-2-methyl heterocycles (121

X = S¹⁴³ and 122 X = Se) by the action of butyllithium followed by dimethyl sulphate at -70°C. Bromination of 121 by using bromine in acetic acid at room temperature gave 2,3-dibromo-5-methylthiophene (123), as described previously.⁶¹

Since some methylselenophene derivatives showed a tendency to decompose under halogenation conditions, somewhat greater care had to be taken with these compounds than with their sulphur analogues. (Cf. the iodination of 2,5-dimethylselenophene p 74 and the bromination of 2-methylselenophene p. 82.) Thus compound 122 was brominated with bromine in a mixture of carbon disulphide and acetic acid at -30°C. The hydrogen bromide formed in the reaction was removed (at least to some extent) by passing a current of nitrogen rapidly through the reaction mixture while it was reaching room temperature. In this way, a 63 % yield of 2,3-dibromo-5-methylselenophene (124) was obtained.

The α -bromine atoms in compounds 123 and 124 were substituted by lithium in halogen-metal exchange reactions with butyllithium. It is well established that an α -bromine undergoes halogen-metal exchange must faster than a β -bromine in the thiophene,¹¹¹ selenophene¹¹² and furan¹⁴⁴ series. By adding the lithiated heterocycles to dimethyl disulphide in ether,¹⁴⁵ 3-bromo-5-methyl-2-methylthiothiophene^{82a} (80) and 3-bromo-5-methyl-2-methylthioselenophene (85) were formed.

Gol'dfarb et al.^{82a} previously synthesized 80 by brominating 2-methyl-5-methylthiothiophene with a bromide-bromate solution. The possible formation of the isomeric 3-bromo-2-methyl-5-methylthiothiophene (88) was not examined and compound 80 was not fully characterized so it was considered more suitable to prepare it free of the isomer by introducing the methylthio group in the last step (cf. Ref. 145). For identification purposes, 5-methyl-2,3-bismethylthiothiophene (83) was prepared by treating 80 with 1 equivalent of butyllithium in hexane at -70°C followed by dimethyl disulphide.

It was possible to metalate compound 121 in the "free" α -position with lithium diisopropylamide in ether at room temperature (a bromination step is thus omitted). Upon carbonation of the lithium heterocycle the acid 125 was obtained in 66 % yield. The metalation procedure was described by Davies and Davies,⁴⁷ who selectively metalated 3-bromothiophene in the

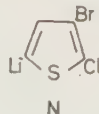
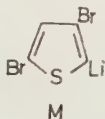
2-position.

By the action of thionyl chloride and pyridine upon 125 in ether, the acid chloride was prepared but was not isolated. After removal of the solvent and excess thionyl chloride, the crude product was directly treated with dimethylamine in benzene to yield the amide 126. Lithium aluminum hydride reduction of 126 gave 3-bromo-5,N,N-trimethyl-2-thenylamine (94) in 21 % yield (based on 125),

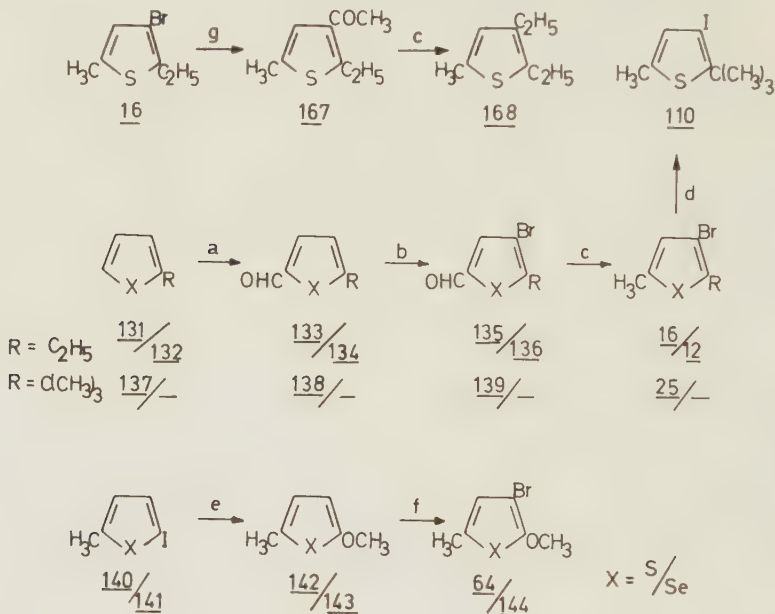
Gjøns and Gronowitz¹⁴⁶ demonstrated that 2-phenylthiophene (127) was brominated with two equivalents of bromine in acetic acid to give 3,5-dibromo-2-phenylthiophene (128). Therefore the synthesis of 3-bromo-5-methyl-2-phenylthiophene (48) was straightforward by the use of butyllithium on 128 followed by dimethyl sulphate. The iodo compound 59 was obtained by treating 48 with butyllithium followed by iodine at -70°C .

Holm^{147a} has recently examined the halogenation of various halogen-substituted thiophene derivatives. It was shown that 3-bromothiophene was predominantly chlorinated in the 2-position by N-chlorosuccinimide to give 3-bromo-2-chlorothiophene^{147a,b} (129), which was brominated in the 5-position by bromine in acetic acid to give 3,5-dibromo-2-chlorothiophene (130). It was possible to prepare 130 by the N-chlorosuccinimide chlorination of 119,^{147a} but by-product formation was considered too unfavorable. By again using the combination butyllithium and dimethyl sulphate, a methyl group was introduced in the 5-position to yield 3-bromo-2-chloro-5-methylthiophene (65).

It should be mentioned that an α -bromine is replaced by lithium far more easily than an α -chlorine in a halogen-metal exchange,^{111,148} even though the lithium compound derived from lithium-chlorine exchange (M) is probably thermodynamically more stable than that obtained from an α -bromine-lithium exchange (N) (cf. Ref. 111b).



Compounds 16 and 25 were prepared as described in Ref. 61, which is indicated in Scheme 12. Essentially the same route was followed for the synthesis of 12, except that butyllithium and dimethylformamide¹⁴⁹ were the reagents for introducing the formyl group in step a, instead of the Vielsmeier formylation.



a) DMF, POCl₃, X = S

BuLi, DMF, X = Se

b) Br₂, AlCl₃

c) N₂H₄, KOH

d) BuLi, I₂, -70°C

e) NaOCH₃, CuO, X = S

NaOCH₃, CuO, HMPT, X = Se

f) NBS, HAc, X = S, X = Se decomp

g) BuLi, DMA

Scheme 12

For kinetic purposes (in this work), 3-iodo-5-methyl-2-t-butylthiophene (110) was prepared. The action of butyllithium on 25 followed by iodine at -70°C gave the desired compound. The bromine atom in compound 16 was replaced by lithium with n-butyllithium and an acetyl group was introduced by adding

N,N-dimethylacetamide to the reaction mixture. The yield of the acetyl derivative 167 was relatively low (42 %), which probably was due to some steric hindrance by the ethyl group. Wolff-Kishner reduction¹⁵⁰ of 167 gave 168.

It is not possible to prepare 2-t-butylselenophene by the method used for the preparation of 2-t-butylthiophene (137) i.e. Friedel-Craft alkylation of thiophene by isobutene and a Lewis acid.¹⁵¹ Such attempts on selenophene have only resulted in decomposition.¹⁵² A possible route to 2-t-butylselenophene would be the addition of hydrogen selenide to 6,6-dimethyl-1,3-hexadiyne, but was not attempted.

Copper-promoted substitution by methoxide ion upon 2-iodo-5-methylthiophene (140) afforded 2-methoxy-5-methylthiophene (142) as described by Sicé et al.⁴⁸ This compound was selectively brominated in the 3-position by N-bromosuccinimide in acetic acid to give 3-bromo-2-methoxy-5-methylthiophene (64).

Attempts to prepare 3-bromo-2-methoxy-5-methylselenophene (144) in the same way as 64 failed. When only a small part of the N-bromosuccinimide was added to 2-methoxy-5-methylselenophene (143) in acetic acid at +17°C, the solution darkened, red elementary selenium precipitated and no trace of the desired compound was detected (vpc). It is quite possible that 144 can be prepared under basic conditions, e.g. by utilizing the method by which 3-bromo-5-methoxy-2-methylthiophene (76) was prepared (cf. Scheme 13). The synthesis of 2-iodo-5-methylselenophene (141) was achieved by using the iodine-iodic acid conditions at room temperature on 2-methylselenophene (81 % yield). The methoxy group was introduced in the same way as in the thiophene case,⁴⁸ i.e. by refluxing 141 in methanol in the presence of excess sodium methoxide and cupric oxide for 6 days. The yield was 23 % of 143. By changing the solvent to hexamethylphosphorus triamide (HMPA), which has a strong solvating power for cations, making the "naked" anions more aggressive, the reaction time was reduced to 48 h and the yield was increased to 47 %. Compound 143 could also be synthesized by O-methylation at the corresponding "hydroxy"selenophene.¹⁵³

Compounds 12, 16, 25, 48, 59, 64, 65, 80, 85, 94 and 110 were all synthesized in order to replace the halogen by lithium and

to study the ring-opening tendency of the lithium compounds. Compounds 83 and 168 were used as reference substances.

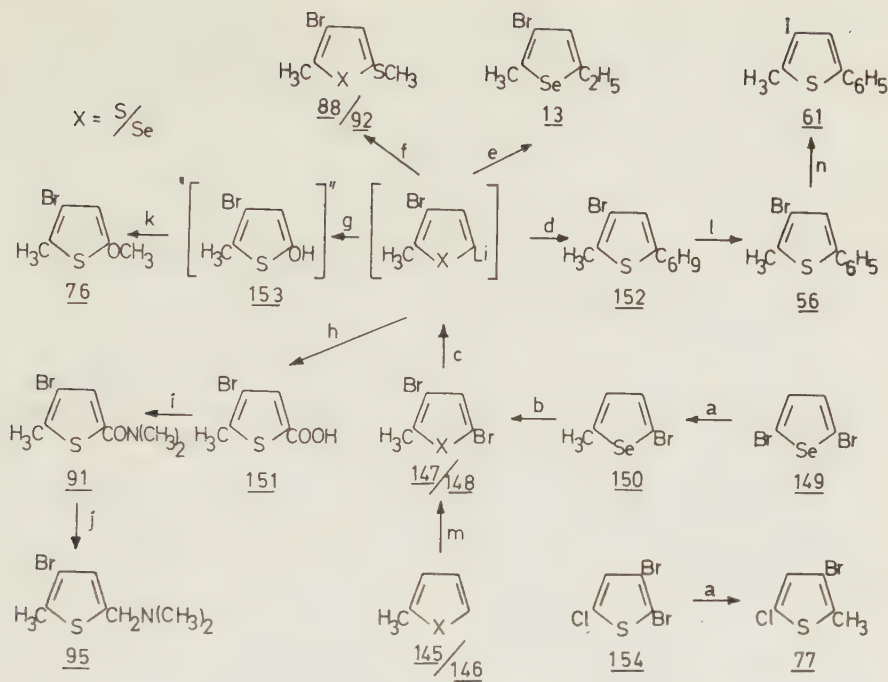
3.3.3 Substances related to 3-halo-2-methyl-substituted heterocycles

Also here the two synthetic routes mentioned previously were utilized. Scheme 13 represents the routes starting with a substance having the halogen in the desired β -position already from the "beginning", and Scheme 14 the routes in which the halogen was introduced at a somewhat later stage. As shown in Scheme 13, 3,5-dibromo-2-methylthiophene (147) was prepared as described by Gronowitz et al.⁸³ from 2-methylthiophene (145) and bromine in acetic acid. When the same procedure was applied to 2-methylselenophene¹²⁷ (146), extensive tar formation took place. The decomposition was almost instantaneous when only a small amount of bromine was added (cf. the attempted preparation of 144, Scheme 12).

It was shown in this work that when 2-bromo-5-methylselenophene (150), prepared from 2,5-dibromoselenophene^{80a} (149) and butyllithium followed by dimethyl sulphate, was brominated under the above conditions, 3,5-dibromo-2-methylselenophene (148) was obtained in a 53 % yield. It was also found that 146 was brominated by two equivalents of N-bromosuccinimide at room temperature in acetic acid to give 148 (55 %).²⁷ These experiments indicated that it was 146 or some intermediate that decomposed in the presence of strong acids (e.g. HBr).

When 146 was treated with bromine at -20°C in carbon disulphide, a brown oil was obtained which darkened rapidly. An exothermic reaction took place when potassium hydroxide pellets were added, and a 41 % yield of 148 could be isolated after distillation (decomposition of 148 took place to a great extent during all attempts of distillation). Thus it seems probable that an addition product was initially formed between 146 and bromine, and that the elimination of hydrogen bromide, at temperatures above -20°C , started the decomposition (cf. Ref. 80a).

From 147, 3-bromo-2-methyl-5-thienyllithium was prepared



- | | |
|--|--|
| a) BuLi, DMS | h) CO ₂ |
| b) Br ₂ , HAC | i) SOCl ₂ , HN(CH ₃) ₂ |
| c) BuLi | j) LiAlH ₄ |
| d) Cyclohexanone | k) DMS, TBA |
| e) Diethyl sulphate, +25°C | l) DDQ |
| f) CH ₃ SSCH ₃ | m) Br ₂ , HAC, X=S; NBS, HAC, X=Se |
| g) B(OC ₄ H ₉) ₃ , H ₂ O ₂ | n) BuLi, I ₂ , -70°C |

Scheme 13

by a halogen-metal exchange with butyllithium. The thienyllithium derivative was the common reagent for the synthesis of the following substances: 3-bromo-2-methyl-5-thiophenecarboxylic acid (151) (with carbon dioxide), 3-bromo-5-(1-cyclohexenyl)-2-methylthiophene (152) (with cyclohexanone¹⁵⁴), 3-bromo-2-methyl-5-"hydroxy"thiophene (153) (with tributylborate and hydrogen peroxide¹⁵⁵) and 3-bromo-2-methyl-5-methylthiophene (88)

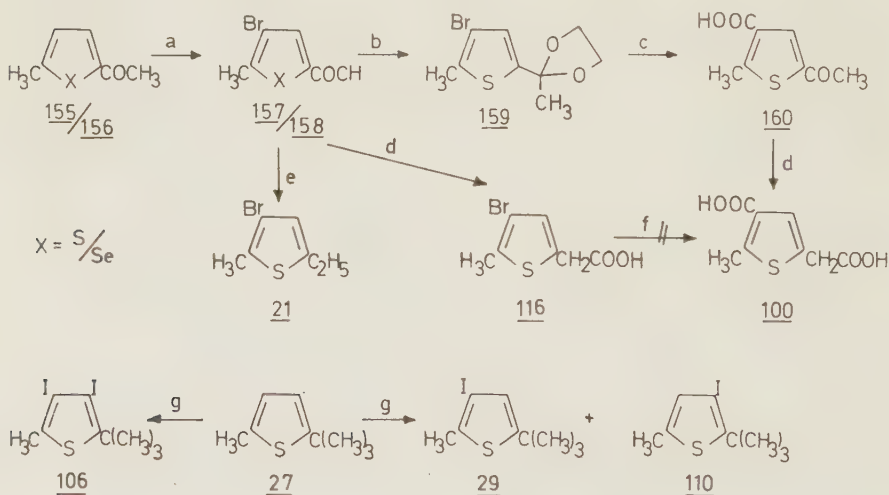
(with dimethyl disulphide¹⁴⁵).

Compound 153 was not isolated in a pure state, but was immediately methylated on oxygen, giving 3-bromo-5-methoxy-2-methylthiophene (76). This was performed by ion pair extraction with dimethyl sulphate as alkylating agent. The method has been developed by Brändström et al.¹⁵⁶ The yield of 76 was 32 % based on 147.

By treating 148 with butyllithium followed by dimethyl disulphide at -70°C , 3-bromo-2-methyl-5-methylthioselenophene (92) was obtained, in analogy with 88.

The acid 151 was converted to its N,N-dimethylamide 91 which was further reduced to 3-bromo-2,N,N-trimethyl-5-thenylamine (95), in the same manner as the 3-bromo-5-methyl isomer (94).

Aromatization of crude 152 was carried out with dichlorodicyanobenzoquinone (DDQ) in benzene to give 3-bromo-2-methyl-5-phenylthiophene (56) in 56 % yield (based on 147). The iodo compound 61 was prepared in the same way as the 4-halo-2-methyl



a) AlCl_3 , Br_2

b) $\text{HOCH}_2\text{CH}_2\text{OH}$, PTS

c) BuLi , CO_2 , HCl

d) TTN, MeOH , OH^-

e) N_2H_4 , KOH

f) EtLi , CO_2

g) I_2 , HIO_3

Scheme 14

isomer 59 (cf. Scheme 11). Since 2,3-dibromo-5-chlorothiophene (154) was available at this institute from the work of Holm,^{147a} 3-bromo-5-chloro-2-methylthiophene (77) was conveniently prepared by performing a halogen-metal exchange upon 154 followed by treatment with dimethyl sulphate.

The synthesis of 3-bromo-5-ethyl-2-methylthiophene (21) (Scheme 14) was described by Hörnfeldt and Lantz⁶¹ who brominated 2-acetyl-5-methylthiophene (155) with bromine and aluminum trichloride (the "swamping" method¹⁵⁷). Subsequent Wolff-Kishner reduction of 157 gave a good yield of 21. This method was also used in this work. Then it seemed natural to apply this route to obtain 3-bromo-5-ethyl-2-methylselenophene (13) as well (Scheme 13). By the "swamping" method, 2-acetyl-5-methylselenophene¹⁵⁸ (156) was converted to 5-acetyl-3-bromo-2-methylselenophene (158) without difficulty. However, when the modified Wolff-Kishner reduction¹⁵⁰ was attempted on 158, no reduction took place. A yellow precipitate was formed when hydrazine was heated together with 158 in ethylene glycol. The subsequent base treatment did not lead to nitrogen evolution, even at 160-180°C. At this temperature red elementary selenium started to form, and therefore the experiment was stopped and a small amount of the yellow crystals was isolated. The largest mass number was around 280, which indicated the presence of the hydrazone of 158. Despite several recrystallizations, the substance was not obtained pure as judged from its broad melting interval. Lithium aluminum hydride reduction of the tosyl hydrazone of 158 was also unsuccessful due to decomposition (red selenium formation).

Instead, 13 was prepared from 148 by halogen-metal exchange followed by diethylsulphate treatment (Scheme 13). Unfortunately, 13 was not obtained pure by distillation or by tlc. The diethyl sulphate, left from the reaction, showed an amazing tendency to adhere to 13. However, it was considered pure enough (90 %, nmr) to be used in the ring-opening experiments.

Ketalization of 157 (Scheme 14) with ethylene glycol afforded the ketal 159, which was treated with butyllithium at -70°C. Subsequent carbonation gave a 76 % yield of 5-acetyl-2-methyl-3-thiophenecarboxylic acid (160) (based on 159).²⁸ Thallium nitrate oxidation¹⁴⁰ of 160 in methanol followed by

basic hydrolysis of the resulting ester gave 3-carboxy-2-methyl-5-thienylacetic acid (100).²⁸

Another route to obtain 100 was attempted, namely the oxidation of 157 with thallium nitrate to give 3-bromo-2-methyl-5-thienylacetic acid (116). This acid was then to be converted to 100 by the use of two equivalents of butyllithium followed by carbonation. It was, however, shown by nmr spectroscopy that the acidic product obtained in the above experiment probably contained a malonic acid. An absorption at $\delta = 4.38$ ppm, which disappeared upon heating the sample was an indication of a methine proton. Furthermore gas evolution took place when the acid mixture was heated in a test tube. Since thienylmalonic acids readily lose carbon dioxide when heated,¹⁵⁹ the above assumption was somewhat justified.

Following the description by Hörnfeldt and Lantz,⁶¹ 5-t-butyl-3-iodo-2-methylthiophene (29) was synthesized from 5-t-butyl-2-methylthiophene (27) by the iodine-iodic acid method.^{135b} It was found that a mixture containing 90 % of 29 and 10 % of its isomer 2-t-butyl-3-iodo-5-methylthiophene (110) was formed (vpc). A convenient way of eliminating this isomer (110) was to treat the mixture with 0.2 equivalent of butyllithium followed by hydrolysis. In this way, 29 was obtained free from the isomer, although some of it (10 %) was lost. It is possible that less than 0.2 equivalent of butyllithium is necessary due to the assumed greater reactivity of the iodine next to the t-butyl group. Steric release might be gained when an iodine atom is replaced by a lithium atom. Such effects have been noticed in other cases, in which a bromine atom next to a t-butyl group was more reactive in halogen-metal exchange than a bromine atom next to a hydrogen.¹⁶⁰

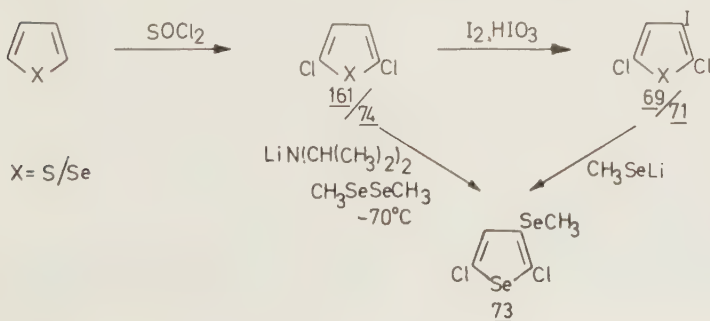
It was also possible to achieve diiodination of 27 with the iodine-iodic acid method.^{135b} Thus 5-t-butyl-3,4-diiodo-2-methylthiophene (106) was prepared in 43 % yield by using two equivalents of iodine (totally) and a prolonged reaction time at 80°C.

Compounds 13, 56, 61, 76, 77, 88, 92, and 95 (Scheme 13), 21, 29, and 106 (Scheme 14) were all prepared to be examined in ring-opening experiments, and 100 was a reference substance.

3.3.4 Substances related to 2,5-dichloro-3-halo heterocycles

Steinkopf and Köhler¹⁶¹ prepared 2,5-dichlorothiophene (161) by the direct chlorination of the thiophene nucleus with elementary chlorine. Subsequently Hartough et al.¹⁶² investigated this reaction in more detail and found that several chlorothiophenes, as well as addition products between chlorine and thiophene, were formed. The method used in this work has been the chlorination of thiophene with sulphuryl chloride without solvent.¹⁶³ From earlier experiments with selenophene, it was known that this heterocycle was somewhat more sensitive towards strong acids (see e.g. the bromination of 2-methylselenophene p. 82) than was thiophene. Since 161 is prepared at reflux temperature of the reaction mixture (initially between 70 and 80°C) it was considered more appropriate to use a solvent in the selenophene case (b.p. 110°C). Benzene was suitable with respect to boiling point (80°C), as well as reactivity. Selenophene is reported to react faster than thiophene in electrophilic aromatic substitution,¹⁶⁴ and thiophene is much more reactive than benzene (by a factor of ~ 1000 or more).^{111b} Thus by using sulphuryl chloride in benzene, 2,5-dichloroselenophene^{80a} (74) was prepared in 47 % yield. It might be advantageous to use benzene in the thiophene case as well.

By applying the iodine-iodic acid method^{135b} to 161 and 74, 2,5-dichloro-3-iodothiophene (69) was obtained in 70 % yield and the selenophene analogue (71) in 66 % yield. Holm isolated a 39 % yield of 69 from the chlorination of 3-iodothiophene with N-chlorosuccinimide.^{147a} Obviously the synthetic route used in this work is preferable for the preparation of 69.



During work with ring-opening experiments, it appeared that 2,5-dichloro-3-selenienyllithium was stable towards ring cleavage when prepared from 74 and lithium diisopropylamide in ether at -70°C , while the contrary was true when 71 was treated with ethyl- or butyllithium under the same conditions (see 2.4). This result was utilized for the preparation of 2,5-dichloro-3-methylselenoselenophene (73). Thus, 74 was metalated at -70°C by lithium diisopropylamide. Introduction of the methylseleno function was accomplished by the addition of dimethyl diselenide¹⁶⁵ to the reaction mixture. In this way a 50 % yield of 73 was obtained. Nucleophilic substitution on 71 by lithium methylselenolate¹⁶⁶ also gave 73. This reaction was, however, incomplete even after several hours at room temperature in ether or in liquid ammonia at -33°C , which possibly was due to heterogeneous systems.

3.3.5 Thiophenophanes

In order to synthesize thiophenophanes two main principles have been used by different workers. (For a review see Ref. 167.)

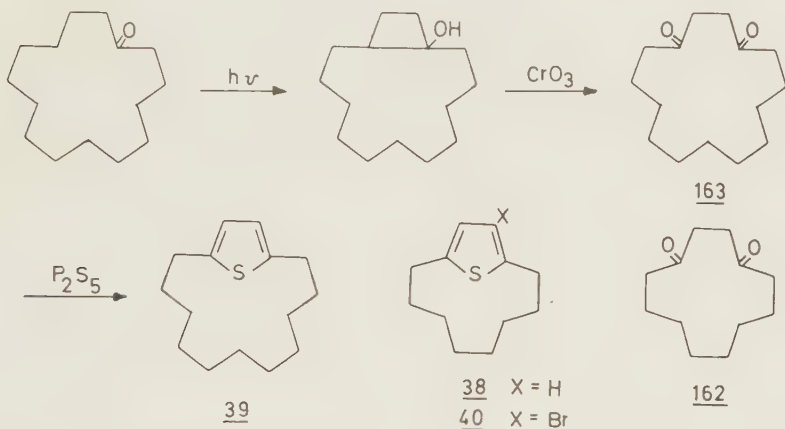
One of these principles was to start with the thiophene nucleus and then to put on side-chains of suitable length. Subsequent cyclization (by various methods) has led to various thiophenophanes. This principle was worked out by Gol'dfarb et al. (see references cited in Ref. 167).

These routes to thiophenophanes were very intriguing and some involved extremely elaborate procedures. Still, further synthetic manipulations would have been necessary to obtain the reduced thiophenophanes.

The other principle for the production of thiophenophanes seemed more convenient and was used in this work. In this case, the thiophene ring was formed in a Paal-Knorr synthesis, starting from a cyclic 1,4-diketone and a sulphur source.

Nozaki et al.⁶⁶ described the synthesis of [8](2,5)-thiophenophane (38) in 51 % yield by simply heating 1,4-cyclododecadiene¹⁶⁸ (162) with phosphorus pentasulphide. Instead of phosphorus pentasulphide, hydrogen sulphide and hydrogen chloride could be used,⁶⁷ which only gave a 20% yield of 38 when applied in these laboratories.

The dione 162 was synthesized in the following way, which was described by Helder.⁶⁷ Cyclododecanone in petroleum ether (60-80) was irradiated with a medium pressure mercury lamp to give 1-hydroxy[0,2,8]bicyclododecane, which was oxidized with "Jones solution"¹⁶⁹ to afford 162. This route was also followed in the preparation of [11](2,5)-thiophenophane (39) from cyclodecapentanone (see below). The yield of 39 was 4 % using HCl/H₂S and 20 % using phosphorus pentasulphide in the cyclization of 1,4-cyclopentadecandione (163). Large amounts of nice-smelling

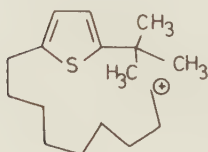


yellow resins were formed in the cyclization of both 162 and 163. The reasons for this is not clear and has not been reported in the literature.

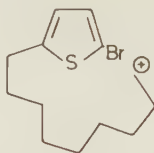
No detectable amounts of 3-bromo-[8](2,5)-thiophenophane (40) were formed when 38 was subjected to various bromination conditions (Br_2 in acetic acid, Br_2 in pyridine, NBS in acetic acid). In one of the experiments (Br_2 in acetic acid), a crude product was obtained, the nmr spectrum of which showed an AB quartet in the aromatic part with a coupling constant $J = 3.4$ Hz. This indicated the presence of an unsymmetrically 2,5-disubstituted thiophene nucleus.

Helder⁶⁷ reported rearrangements of 38 in Friedel-Craft t-butylation experiments. It was shown that 38 formed 5-t-butyl-[8](2,4)-thiophenophane together with other rearranged substances upon treatment with t-butylchloride and stannic chloride in carbon disulphide at room temperature.

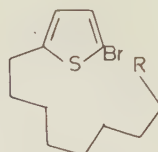
It may be suggested that the above rearrangements might involve carbonium ions such as 164 and 165. Accordingly,



164



165



166
R = Br;CH₃COO

structures such as 166 might be responsible for the presence of the suggested unsymmetrically 2,5-disubstituted thiophene derivative mentioned above. The different fates of 164 and 165 should depend on the reaction conditions, e.g. the availability of nucleophiles.

The bromination of 39 with bromine in acetic acid was somewhat more successful. Vpc analysis of the crude product showed the presence of three components in the proportions 2:2:5 (increasing retention times). The latter was the desired 3-bromo-[11](2,5)-thiophenophane (41), which was isolated in a 25 % yield. No attempts were made to elucidate the identities of the other two compounds.

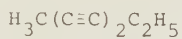
3.4 2,4-Heptadiyne

A number of workers have prepared 2,4-heptadiyne (109) by several methods.¹⁷⁰⁻¹⁷² However, the yields were low and the substance was fully characterized by Cadiot et al.¹⁷² as late as in 1963.

The synthesis of diacetylene from 1,4-dichloro-2-butyne was demonstrated by Armitage et al.,¹⁷³ who used sodium in liquid ammonia for the elimination of hydrogen chloride. The alkylation of the diacetylene anion gave various mono- and di-substituted diacetylenes, depending on the conditions.

A detailed description of the preparation of 1,3-hexadiyne starting from 1,4-dichloro-2-butyne was found in Ref. 84c. In this case, three equivalents of sodium amide in liquid ammonia were used as base and the diacetylene monoanion was alkylated

with diethyl sulphate. By subsequent anion formation of 1,3-hexadiyne with butyllithium and methylation with methyl iodide, 109 was obtained in a 59 % yield.



109

4. SUMMARY

The synthetic value of 3-lithio heterocycles when used at temperatures around -70°C is well known.^{111,112} However, only little is reported about the reactions of these species at higher temperatures. It was therefore of interest to examine the thermal stability of various 3-thienyl, 3-selenienyl and some 3-furyllithium derivatives.

It was found that 3-thienyllithium derivatives (obtained from halogen-metal interconversions between 3-bromo or 3-iodo heterocycles and ethyllithium or phenyllithium) with +I substituents (alkyl, see 2.1) or weak -I substituents (phenyl, see 2.3 and methylthio, see 2.4) in the 2- or 5-positions underwent ring-cleavage in ether at $+21^{\circ}\text{C}$. The primary reaction products, the enyne thiolates, could be trapped by alkylation at sulphur by various alkyl halides. If water was added, ring-closure took place to give the dehalogenated heterocycles (Scheme 3).

In cases where more powerful -I, +M substituents (chlorine and methoxy, see 2.4) were situated in the 2-position, the 3-thienyllithium derivatives appeared to be quite stable at room temperature, since these species could be trapped with dimethyl sulphate or solid carbon dioxide. (This could not be realized when the ring-opening was fast.) The resistance toward ring-cleavage was attributed to the strong -I effect and/or the existence of non-bonded electron pairs. The stability of 2-N,N-dimethylaminomethyl-5-methyl-3-thienyllithium was explained by an intramolecular complex, which indicated that this could be enough to prevent the thienyllithium derivatives from undergoing ring-cleavage (see 2.5).

The stabilizing effects of the methoxy, chloro and N,N-dimethylaminomethyl groups was lost when these substituents were placed in the 5-position, which made it possible to isolate the corresponding enynes (see 2.4 and 2.5). In the case of 5-chloro-2-methyl-3-thienyllithium further elimination of hydrogen chloride led to the formation of 1-ethylthio-1,3-pentadiyne.⁸¹

Attempts to isolate definite products from the decomposition of 3-furyllithium failed due to polymerization. It was, however, possible to isolate an acetylenic ketone (36) from the ring-opening of 2,5-dimethyl-3-furyllithium at 0°C (see 2.1.1).

The temperature necessary for a convenient ring-opening of 2,5-dimethyl-3-thienyllithium was above 0°C, while the selenium counterpart ring-opened rapidly even at -70°C (see 2.1.1). The greater tendency of 3-selenienyllithium derivatives to be cleaved was also noticed in the case of 2,5-dichloro-3-selenienyllithium, which also ring-opened at -70°C (see 2.4). One would expect this substance to be more stable, in analogy with its thiophene counterpart. It is possible that the ring-opening mechanisms in the thiophene and in the selenophene series are different.

The metalation of 2,5-dimethylthiophene and tetramethylthiophene with alkyllithium:TMEDA complexes took place in the (α -) side-chains and also in the aromatic nucleus of the former compound (see 2.6). Acetylenes were formed in both cases, which indicated that not only 3-thienyllithium derivatives, but 2-thienyllithium derivatives as well, were subjected to ring-cleavage.

Kinetic measurements by the nmr technique revealed that the ring-opening was pseudo first-order with respect to the 3-thienyllithium derivatives. It was also shown that bulky substituents, especially in the 4- and 5-positions, decreased the reaction rate.

From a synthetic point of view, the ring-opening reaction examined in this work may be of value, e.g. when conjugated vinylacetylenic seleno- and thioethers with specific stereochemistry are desired, since the ring-cleavage proceeds in a trans fashion. Thus, it was demonstrated that mixed acetylenic monothio-, dithio- and thio-seleno keteneacetals with specific stereochemistry could be synthesized in fair yields (2.4). A synthetic route to fully substituted vinylacetylenic thioethers was opened by performing ring-opening experiments on 2,4,5-trimethyl-3-thienyllithium and 2,5-dimethyl-4-phenyl-3-thienyllithium (2.1.1 and 2.3). By performing the ring-opening reaction on 3-lithio-[11](2,5)-thiophenophane the macrocyclic (fifteen-membered) conjugated vinylacetylenic ethylthio-ether was obtained (2.1.2). The ring-opening reaction thus corresponds to the regio- and stereospecific addition of thiolates to unsymmetrically substituted diacetylenes, except in the cases with fully substituted vinylacetylenic thioethers, in which the possibility of addition is excluded. The reactions examined bear some similarity to the reversal of the biosynthesis of

thiophenes as described by Bohlmann et al.,⁴³ and to the reversal of the thiophene synthesis from hydrogen sulphide and diacetylenes.¹³⁸

Mass spectra were of value for structure determination and some features of the fragmentations are discussed (see 2.9). Nmr spectra (^1H , ^{13}C , ^{77}Se) have also been used for structure determination, but are only discussed in some special cases. Both ^{13}C and ^{77}Se nmr measurements of heterocyclic compounds are in progress in these laboratories.

In order to carry out the ring-opening experiments, several 3-halo-2,5-disubstituted thiophene and selenophene derivatives were synthesized, and it was noted that more care had to be used in handling the selenophene derivatives than the thiophene derivatives, presumably due to the greater acid sensitivity of the former (see 3).

5. EXPERIMENTAL

General remarks

All experiments with organometallic compounds were performed under a dry oxygen-free nitrogen atmosphere and in solvents (ether, hexane), which were dried and distilled with sodium wire. The nitrogen gas was bubbled through a wash bottle with a basic pyrogallol solution to remove oxygen and then a wash bottle with conc. sulphuric acid to remove moisture. Hexamethylphosphorus triamide (HMPA) was purified according to Ref. 84a. Dimethyl sulphate (DMS) and dimethyl formamide (DMF) were used freshly distilled, and the iodobenzene (used for the phenyllithium preparations) was distilled twice with an efficient column.

The ethereal metal-organic reagents (CH_3Li , $\text{C}_2\text{H}_5\text{Li}$, $\text{C}_6\text{H}_5\text{Li}$ and $\text{C}_4\text{H}_9\text{Li}$) were all titrated on the total base content with 0.1M HCl and the real titre of the ethyllithium and n-butyllithium solutions was obtained by the double titration procedure.⁹⁷

Vpc analyses were performed with a Perkin-Elmer 900 gas chromatograph or a Varian 1400 gas chromatograph, both equipped with flame ionization detectors. The areas of the peaks of the gas chromatograms were evaluated with a Varian 480 digital integrator connected to the PE 900 or simply by the triangle approximation. It appeared that the discrepancy between the two methods was less than ± 5 rel %, which was considered small, since calibration was not performed in any case. However, the chromatograms could be reproduced within ± 2 rel %, and therefore fairly accurate comparisons of changes in the product distributions could be made. The columns were made of stainless steel (2.0 mm i.d., 1.9 m) and nitrogen was used as carrier gas (flow rate 35 ml/min). The carriers for the stationary phases were Chrom. W (80/100, for NPGS and BDS), Gas Chrom. Q (80/100, for OV17 and OV 1) and Diatomite ClQ (100/120, for SE 30). For preparative vpc a Perkin-Elmer F 21 preparative gas chromatograph was used, equipped with a 20 % BDS column (8.0 mm i.d., 2.7 m).

Mass spectra were recorded on a LKB 9000 mass spectrometer with an ionization energy of 70 eV. ^1H nmr spectra were in most cases recorded on a Varian A-60 nmr spectrometer, and in a few cases on a Varian XL 100-15 nmr spectrometer. The ^{13}C nmr spectrum was recorded on a Jeol FX-60 nmr spectrometer and the ^{77}Se nmr spectra on a Varian XL 100-15 nmr spectrometer.

The nmr spectra have been subjected to first-order treatment. Ir spectra were recorded on a Perkin-Elmer Grating Infrared spectrometer and an Unicam SP 800 spectrophotometer. The melting points were determined with a Reichert melting point microscope and are uncorrected. Elemental analyses were performed by the Department of Analytical Chemistry at the University of Lund, Miss Ilse Beetz, Mikroanalytisches Laboratorium, Kronach, West Germany and by Dornis und Kolbe, Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, West Germany.

The isolations of the pure acetylenic derivatives were in most cases performed by tlc. Glass plates with an activated 1 mm silica gel layer (Kieselgel GF 254 nach Stahl, 10-40 μ , Merck) were used, and the crude products were applied on the plates as 50 % acetone solutions by the aid of a Camag Chroma-tocharger. The zones were made visible with a uv lamp (360 nm) and eluted with ether. The purity of the substances was checked with vpc, nmr and elemental analyses.

Experimental part of Chapter 2.1

General method for the ring-opening of 3-lithioheterocycles (G)

Nitrogen gas was supplied for 30 min to the predried, hot (110°C) apparatus, consisting of a three-necked round-bottomed flask fitted with a condenser (drying tube, CaCl_2), stirrer, dropping funnel and a neck for the gas inlet. The dropping funnel was also supplied with nitrogen gas. The 3-halo heterocyclic compound was dissolved in ether and ethereal ethyllithium was added rapidly. After 10 min, an excess of ethyl bromide or iodide was added all at once, and the reaction mixture was kept at +21°C (room temperature) for 4 h. The reaction mixture was hydrolyzed with water and the aqueous phases were extracted three times with ether. The collected ethereal portions were washed with water to neutral reaction and dried with MgSO_4 . After the evaporation of the solvent the crude product was purified by distillation or by tlc.

Attempted preparation of 2,2',5,5'-tetramethyl-3,3'-biselenienyl

To 5.00 g (0.0175 mol) of 2,5-dimethyl-3-iodoselenophene (1) in 15 ml of ether, 20 ml (0.023 mol) of 1.13 M ethereal

ethylolithium was added dropwise at -70°C . After 10 min, 2.40 g (0.0179 mol) of dry CuCl_2 was poured (in portions) into the reaction mixture. (The cupric chloride was placed in an Erlenmeyer flask connected to the reaction vessel with a piece of rubber tubing.) The reaction mixture was kept at -70°C for 4 h with stirring. It was then warmed to -10° , whereupon 25 ml of 2.5 M HCl was added. The ethereal phase was washed with ether, 2.5 N HCl, water and dried. After evaporation of the ether, 3.50 g of crude product remained, which was analyzed by vpc-ms (column OV1, 3%, $100-250^{\circ}\text{C}$, $10^{\circ}/\text{min}$). Two components appeared, the most volatile of which was 2,5-dimethylselenophene, while the other had $m/e = 318$ (2 Se). Attempted distillation of the crude product gave a yellowish, evil smelling oil, b.p. $120-155^{\circ}\text{C}$, that mainly contained the compound with $m/e = 318$ (extensive decomposition took place during the distillation). Ir spectra of the crude product and of the distillate: $\text{C}\equiv\text{C}$, 2220 cm^{-1} .

A brown solid was also isolated from the reaction mixture. It was insoluble in ether, CCl_4 , acetone and water. Mass spectrum: $m/e = 381$ (2 Se), base peak at $m/e = 318$ (loss of ^{63}Cu). Ir: $\text{C}\equiv\text{C}$, 2220 cm^{-1} . The brown solid was treated with a conc. NH_4OH solution and the blue aqueous phase was extracted with petroleum ether (40-60). After drying and evaporation, a small amount of a yellowish oil remained, which mainly consisted of a component with the same retention time as the component with $m/e = 318$. Ir: $\text{C}\equiv\text{C}$, 2220 cm^{-1} . (For structure suggestions see chapter 2.1.) Traces of the biselenienyl could not be detected.

2,5-Dimethyl-3-selenophenecarboxylic acid⁵³ (4)

a) The Grignard reagent was prepared in the usual manner from 112 g (0.393 mol) of 2,5-dimethyl-3-iodoselenophene¹ (1) in 250 ml of ether, 10.8 g (0.444 mol) of magnesium and 1 ml of ethyl bromide. When spontaneous reflux had stopped, the mixture was refluxed for 1/2 h and then poured onto solid carbon dioxide in ether. When the mixture had reached room temperature, 200 ml of 1 N HCl was added. The ether phase was separated and the aqueous layer was extracted several times with ether. The combined ethereal phases were extracted with 0.5 N KOH solution. Upon acidification of the combined alkaline solutions with 2.5 N HCl, 45 g of crude acid was precipitated. Recrystallization from acetic acid:water:methanol (1:20:4) yielded 41.5 g (52 %) of the

title compound, m.p. 117-118°C (lit.⁵³ m.p. 118.5°C). Nmr (CDCl₃): $\delta_{2\text{CH}_3} = 2.77$ ppm (s, 3H); $\delta_{5\text{CH}_3} = 2.47$ ppm (bs, 3H); $\delta_{4\text{H}} = 7.29$ ppm (q, 1H). $J_{5\text{CH}_3, 4\text{H}} = 1.2$ Hz.

b) To 5.00 g (0.0175 mol) of 1 in 25 ml of ether cooled to -100°C, 22 ml (0.024 mol) of 1.10 M ethyllithium was added dropwise with stirring. After stirring for an additional 15 min, powdered carbon dioxide was added at such a rate that the temperature did not rise above -100°C. Analogous work-up as described above yielded 1.82 g (51 %) of the title compound with the same physical properties (m.p., ir spectrum). 1.42 g of 1 was recovered.

c) When 1 was treated as in b) but at -70°C, no carboxylic acid could be isolated after carbonation. The neutral ether phase contained acetylenes, as indicated by an ir spectrum; $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Vpc analysis (column BDS, 10 %, 80-200°C, 10°/min) showed the presence of 2,5-dimethylselenophene (> 90 %) and several other components.

(Z)-2-Ethylseleno-2-hexen-4-yne² (5). The general method (G) was followed. From 5.00 g (0.0175 mol) of 2,5-dimethyl-3-iodo-selenophene (1), 20 ml of ether, 20 ml (0.019 mol) of 0.95 M ethereal ethyllithium and 9.5 g (0.087 mol) of ethyl bromide, a 70 % yield (2.3 g) of the title compound was isolated through distillation, b.p._{0.2} 49-51°C (nitrogen swept distillation apparatus). The dried ethereal phase from the reaction mixture was analyzed by combined vpc-ms (column BDS, 10%, 100-180°C, 8°/min), and contained almost only 5 (m/e = 188; calc. for C₈H₁₂⁸⁰Se = 188). For fragmentation see 2.9, Table 3. Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Nmr (CCl₄): $\delta_{1\text{H}} = 2.12$ ppm (m, 3H); $\delta_{3\text{H}} = 5.58$ ppm (m, 1H); $\delta_{6\text{H}} = 1.98$ ppm (m, 3H); $\delta_{\text{SeCH}_2\text{CH}_3} = 2.79$ ppm (q, 2H) and 1.40 ppm (t, 3H). $J_{\text{SeCH}_2-\text{CH}_3} = 7.5$ Hz; $J_{1\text{H}, 6\text{H}} = 0.6$ Hz; $J_{1\text{H}, 3\text{H}} = 1.2$ Hz; $J_{3\text{H}, 6\text{H}} = 2.4$ Hz. The coupling constants are the splittings of the peaks and do not represent the true coupling constants. (Cf. p 18.) [Found: C 51.00; H 6.52. Calc. for C₈H₁₂Se (187.14): C 51.34; H 6.46.]

When the reagents were mixed at -70°C and the reaction mixture was thereupon allowed to reach room temperature and hydrolyzed after 4 h, the dried ethereal phase contained 25 %

of 2,5-dimethylselenophene and 75 % of 5 (vpc - conditions as above). After distillation, a 50 % yield of 5 and a 10 % yield of 2,5-dimethylselenophene (b.p.₁ < 60°C) were isolated.

2,5-Dimethyl-3-thiophenecarboxylic acid. Ethereal methyl-lithium (50 ml, 0.70 M) was added dropwise under nitrogen with stirring to a solution of 5.00 g (0.0210 mol) of 2,5-dimethyl-3-iodothiophene in 40 ml of anhydrous ether cooled to -70°C. The mixture was allowed to stand at -70°C for 6 h and was then carbonated. The usual work-up yielded 2.51 g (77 %) of 2,5-dimethyl-3-thiophenecarboxylic acid, m.p. 117-118°C (lit.¹⁷⁴ m.p. 119-120°C).

The neutral phase contained 0.35 g of a mixture of 2,5-dimethylthiophene and 2,5-dimethyl-3-iodothiophene, but no ring-opened product (ir).

The reaction between 2,5-dimethyl-3-iodoselenophene and phenyllithium. To 31.5 ml (0.030 mol) of 0.95 M ethereal phenyllithium, 8.3 g (0.029 mol) of 2,5-dimethyl-3-iodoselenophene in 50 ml of ether was added at room temperature. After 1.5 h, crushed solid carbon dioxide was added to the reaction mixture, which then was extracted with 2 N NaOH. The collected aqueous solutions were acidified and extracted with ether, which was then evaporated. Only 0.1 g of a brown liquid remained. The neutral ethereal phase from the reaction mixture was analyzed by vpc (column BDS, 10%, 110°C), which showed the presence of 2,5-dimethylselenophene (111) and iodobenzene (1:1).

(Z)-2-Ethylthio-2-hexen-4-yne^{44a} (9). The general method G was followed. From 23.8 g (0.100 mol) of 2,5-dimethyl-3-iodothiophene (8) in 200 ml of ether, 115 ml (0.10 mol) of 0.85 M ethyllithium and 32.7 g (0.300 mol) of ethyl bromide, 7.0 g (50 %) of the title compound was isolated through distillation, b.p.₁₂ 94-98°C (some decomposition), n_D^{25} 1.5451 (lit.^{44a} 70 % yield, b.p._{1.0} 54°C, n_D^{20} 1.5511). Mass spectrum: m/e = 140. Calc. for C₈H₁₂S = 140. For fragmentation see 2.9, Table 3. NMR (CCl₄): δ_{1H} , δ_{6H} = 1.96 ppm (m, 6H); δ_{3H} = 5.32 ppm (m, 1H); $\delta_{SC_2H_5}$ = 2.80 ppm (q, 2H) and 1.25 ppm (t, 3H). $J_{SCH_2-CH_3}$ = 7.0 Hz.

(Z)-2-Methylseleno-2-hexen-4-yne (10). To a solution of 15.0 g (0.0526 mol) of 2,5-dimethyl-3-iodoselenophene (1) in

100 ml of ether cooled to -110°C , 100 ml (0.060 mol) of 0.60 M methylolithium was added at such a rate that the temperature did not exceed -100°C . When the addition was complete 35.5 g (0.25 mol) of methyl iodide was added and the reaction mixture was allowed to reach room temperature and poured into water. The ether phase was separated and the aqueous layer extracted with ether. The combined ethereal portions were washed with water and dried. Evaporation of the solvent yielded 7.5 g (82 %) of the crystalline title compound, which according to vpc-ms analysis (column BDS, 10%, $80-170^{\circ}\text{C}$, $10^{\circ}/\text{min}$) was homogeneous; $m/e = 174$. Calc. for $\text{C}_7\text{H}_{10}^{80}\text{Se} = 174$.

Recrystallization from aqueous ethanol gave the pure title compound, m.p. $29-30^{\circ}\text{C}$. Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} , $\text{C}=\text{C}$ 1590 cm^{-1} . Nmr (CCl_4): $\delta_{6\text{H}} = 1.97\text{ ppm}$ (d, q, 3H); $\delta_{1\text{H}} = 2.10\text{ ppm}$ (m); $\delta_{3\text{H}} = 5.55\text{ ppm}$ (m, 1H); $\delta_{\text{SeCH}_3} = 2.13\text{ ppm}$ (s). $J_{1\text{H}, 6\text{H}} = 0.6\text{ Hz}$; $J_{3\text{H}, 6\text{H}} = 2.4\text{ Hz}$. [Found: C 48.94; H 5.86. Calc. for $\text{C}_7\text{H}_{10}\text{Se}$ (173.12): C 48.57; H 5.82.]

(Z)-2-Methylthio-2-hexen-4-yne (11a).

a) To a solution of 10.0 g (0.0420 mol) of 2,5-dimethyl-3-iodothiophene (8) in 40 ml of ether, 60 ml (0.042 mol) of 0.70 M methylolithium was added at room temperature. The mixture was refluxed for 2 h, cooled, poured into water and worked-up as above. Combined vpc-ms analysis (column BDS, 10 %, $80-170^{\circ}\text{C}$, $10^{\circ}/\text{min}$): $m/e = 126$. Calc. for $\text{C}_7\text{H}_{10}\text{S} = 126$. The molecular ion was the base peak. Fractionation yielded 0.73 g (14 %) of 2,3,5-trimethylthiophene, b.p.₁₄ $60-65^{\circ}\text{C}$, identified by combined vpc-ms (as above), and 2.26 g (42 %) of the title compound, b.p.₁₄ $89-90^{\circ}\text{C}$, m.p. $34-35^{\circ}\text{C}$. Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} , $\text{C}=\text{C}$ 1590 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}, 6\text{H}} = 1.98\text{ ppm}$ (m, 6H); $\delta_{3\text{H}} = 5.25\text{ ppm}$ (m, 1H); $\delta_{\text{SCH}_3} = 2.28\text{ ppm}$ (s, 3H). [Found: C 66.62; H 8.05; S 25.08. Calc. for $\text{C}_7\text{H}_{10}\text{S}$ (126.22): C 66.61; H 7.99; S 25.40.]

b) To 100 ml (0.10 mol) of 1.0 M ethereal phenyllithium, 23.8 g (0.100 mol) of 8 in 100 ml of ether was added at room temperature. After 1/2 h, 13.9 g (0.110 mol) of DMS in 50 ml of ether was slowly added. Ammonium hydroxide solution was added after 1 h and the ethereal layer was washed with water, 2 N HCl and water to neutral reaction. After drying and evaporation of the solvent, the residue was distilled, to yield 7.9 g (63 %)

of the title compound with the same properties as described above (nmr, ir, m.p.).

The reaction between 2,5-dimethyl-3-bromothiophene and methyllithium. A solution of 15.0 g (0.0785 mol) of 2,5-dimethyl-3-bromothiophene in 100 ml of ether was cooled to -70°C , whereupon 100 ml (0.0810 mol) of 0.81 M methyllithium was added dropwise, followed by 5.68 g (0.0400 mol) of methyl iodide. The mixture was then allowed to reach room temperature. A sample was poured onto solid carbon dioxide in ether but no carboxylic acid could be isolated. After 21 h, water was added to the reaction mixture and the ethereal layer was washed with water and dried. Vpc analysis (column BDS, 10 %, 105°C) showed, upon comparison of the retention times with authentic samples, that the starting material amounted to ~ 90 % and compound 11a to ~ 10 %. Ir of the evaporated crude product: $\text{C}\equiv\text{C}$ 2220 cm^{-1} .

(Z)-2-Hexen-4-yne-2-yl-thioacetic acid (11b). To 100 ml (0.100 mol) of 1.0 M phenyllithium, 23.8 g (0.100 mol) of 2,5-dimethyl-3-iodothiophene (8) in 100 ml of ether was added at room temperature. After 1/2 h the reaction mixture was pressed over (with nitrogen gas) to a dropping funnel and added to a solution of 16.7 g (0.100 mol) of ethyl bromoacetate in 100 ml of ether (water cooling). The reaction mixture was stirred for 1 h at room temperature, whereupon it was poured into 500 ml of 2 N NaOH and stirred for 2 h. The aqueous layer was separated, extracted with ether and acidified with 5 N HCl. An oil precipitated, which subsequently crystallized. Thus, 10.7 g of the crude title compound was collected by filtration. The pure acid, 9.8 g (58 %), was obtained after recrystallization from ethanol:water, m.p. $84.5\text{--}86.5^{\circ}\text{C}$. Ir: $\text{C}=\text{O}$ 1700 cm^{-1} , $\text{C}\equiv\text{C}$ 2210 cm^{-1} . Nmr (CDCl_3): $\delta_{\text{4H}} = 5.50\text{ ppm}$ (m, 1H); $\delta_{\text{C}=\text{CCH}_3} = 2.08\text{ ppm}$ (m); $\delta_{\text{C}\equiv\text{CCH}_3} = 2.01\text{ ppm}$ (bd); $\delta_{\text{-CH}_2\text{-}} = 3.65\text{ ppm}$ (s, 2H); $\delta_{\text{COOH}} = 11.87\text{ ppm}$ (s, 1H). [Found: C 56.51; H 5.95; S 18.83. Calc. for $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$ (170.23): C 56.45; H 5.92; S 18.84.]

(Z)-2-Benzylthio-2-hexen-4-yne⁵⁹ (11c). With the same amounts of reagents as above, the title compound was prepared by replacing ethyl bromoacetate with 13.9 g (0.110 mol) of benzyl chloride in 50 ml of ether. The reaction mixture was stirred overnight and was subsequently hydrolyzed. The ethereal layer

was washed with water and dried. After evaporation of the solvent, the residue was distilled to give 10.5 g (52 %) of 11c, b.p. $2.0^{141-142^{\circ}\text{C}}$, m.p. $53-55^{\circ}\text{C}$ (lit.⁵⁹ m.p. 55°C). Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Nmr (CCl_4): $\delta_{\text{C}_6\text{H}_5} = 7.0-7.5\text{ ppm (m, 5H)}$; $\delta_{-\text{CH}_2-} = 3.97\text{ ppm (s, 2H)}$; $\delta_{4\text{H}} = 5.32\text{ ppm (m, 1H)}$; $\delta_{1\text{H}}, \delta_{6\text{H}} = 1.93\text{ ppm (bs, 6H)}$.

(Z)-2-Ethylseleno-2-hepten-4-yne (14). The general method G was followed. The title compound was prepared from 2.52 g (0.0100 mol) of 3-bromo-2-ethyl-5-methylselenophene (12) in 50 ml of ether, 17 ml (0.010 mol) of 0.60 M ethereal ethyllithium and 5.45 g (0.0500 mol) of ethyl bromide. Combined vpc-ms analysis (column BDS, 10 %, 170°C) of the washed and dried ethereal solution showed 98 % of 14, m/e = 202. Calc. for $\text{C}_9\text{H}_{14}^{80}\text{Se} = 202$. For fragmentation see 2.9, Table 3. B.p.₁₂ $108-109^{\circ}\text{C}$, 1.1 g (54 %). (The product was distilled from paraffin oil to prevent decomposition of the enyne to some extent.) Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 2.13\text{ ppm (m, 3H)}$; $\delta_{3\text{H}} = 5.58\text{ ppm (m, 1H)}$; $\delta_{6\text{H}} = 2.35\text{ ppm (bq)}$; $\delta_{7\text{H}} = 1.67-0.92\text{ ppm}$, $\delta_{\text{SeC}_2\text{H}_5} = 2.78\text{ ppm (q, 2H)}$ and $1.67-0.92\text{ ppm}$. $J_{\text{SeCH}_2-\text{CH}_3} = J_{6\text{H}, 7\text{H}} = 7.0\text{ Hz}$. [Found: C 53.70; H 7.10; Se 39.25. Calc. for $\text{C}_9\text{H}_{14}\text{Se}$ (201.16): C 53.73; H 7.01; Se 39.25.]

(Z)-3-Ethylseleno-3-hepten-5-yne (15). As above, the title compound was prepared from 2.45 g (9.60 mmol) of 3-bromo-5-ethyl-2-methylselenophene (13) in 50 ml of ether, 16 ml (9.6 mmol) of 0.60 M ethereal ethyllithium and 5.45 g (50.0 mmol) of ethyl bromide. Combined vpc-ms analysis (column BDS, 10 %, 170°C) of the washed and dried ethereal solution showed about 90 % of 15, m/e = 202. Calc. for $\text{C}_9\text{H}_{14}^{80}\text{Se} = 202$. For fragmentation see 2.9, Table 3. B.p.₁₂ $107-108^{\circ}\text{C}$, 1.2 g (60 %). (The distillation was performed from paraffin oil.) Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 1.67-0.83\text{ ppm}$; $\delta_{2\text{H}} = 2.33\text{ ppm (q)}$; $\delta_{4\text{H}} = 5.67\text{ ppm (m)}$; $\delta_{7\text{H}} = 1.95\text{ ppm (m)}$; $\delta_{\text{SeC}_2\text{H}_5} = 2.77\text{ ppm (q)}$ and $1.67-0.83\text{ ppm}$. $J_{\text{SeCH}_2-\text{CH}_3} = J_{1\text{H}, 2\text{H}} = 7.0\text{ Hz}$. [Found: C 53.67; H 6.89; Se 39.22. Calc. for $\text{C}_9\text{H}_{14}\text{Se}$ (201.16): C 53.73; H 7.01; Se 39.25.]

(Z)-2-Ethylthio-2-hepten-4-yne (17). The general method G was followed. From 10.3 g (0.0500 mol) of 3-bromo-2-ethyl-5-methylthiophene (16) in 100 ml of ether, 100 ml (0.060 mol) of 0.60 M ethereal ethyllithium and 39.0 g (0.250 mol) of ethyl

iodide, 4.6 g (60 %) of the title compound was obtained by distillation, b.p.₁₂ 106-107°C. Combined vpc-ms analysis (column BDS, 10 %, 130°C) of the washed and dried reaction mixture showed the following compounds: 17 (m/e = 154; calc. for C₉H₁₄S = 154), 18 (m/e = 182; calc. for C₁₁H₁₈S = 182), 19 (m/e = 126; calc. for C₇H₁₀S = 126) and 20 (m/e = 154; calc. for C₉H₁₄S = 154). See Scheme 4, condition I and for fragmentation see 2.9, Table 3. Ir: C≡C 2220 cm⁻¹. Nmr (CCl₄): δ_{1H} = 1.99 ppm (m, 3H); δ_{3H} = 5.32 ppm (m, 1H); δ_{6H} = 2.32 ppm (bq); δ_{7H} = 1.37-1.05 ppm; δ_{SC₂H₅} = 2.81 ppm (q) and 1.37-1.05 ppm. J_{SCH₂-CH₃} = J_{6H, 7H} = 7.0 Hz. [Found: C 70.10; H 9.13; S 20.71. Calc. for C₉H₁₄S (154.28): C 70.07; H 9.15; S 20.78.] The reaction was repeated, but ethyl iodide was not added to the reaction mixture, which changed the component distribution of the reaction product as shown in Scheme 4, condition II.

(Z)-3-Ethylthio-3-hepten-5-yne (22). The general method G was followed, and the same amounts of reagents as in the preceding experiment were used. Thus, 4.9 g (64 %) of 22, b.p._{2.0} 74-75°C was obtained from 3-bromo-5-ethyl-2-methylthiophene (21). Combined vpc-ms analysis (column BDS, 10 %, 130°C) of the washed and dried reaction mixture showed the following compounds: 22 (m/e = 154; calc. for C₉H₁₄S = 154), 23 (m/e = 182; calc. for C₁₁H₁₈S = 182), 19 (m/e = 126; calc. for C₇H₁₀S = 126) and 24 (m/e = 154; calc. for C₉H₁₄S = 154). See Scheme 4, condition I and for fragmentation see 2.9, Table 3. Ir: C≡C 2220 cm⁻¹. Nmr (CCl₄): δ_{1H} = 1.38-0.97 ppm; δ_{2H} = 2.25 ppm (q); δ_{4H} = 5.39 ppm (m, 1H); δ_{7H} = 1.98 ppm (d); δ_{SC₂H₅} = 2.80 ppm (q, 2H) and 1.38-0.97 ppm. J_{SCH₂-CH₃} = J_{1H, 2H} = 7.0 Hz. [Found: C 70.21; H 9.17; S 20.65. Calc. for C₉H₁₄S (154.28): C 70.07; H 9.15; S 20.78.]

During the distillation, a few mg of almost pure (Z)-3-ethylthio-3-nonen-5-yne (23) was collected at 88-89°C, 2.0 mm Hg. Nmr (benzene, XL-100 spectrum): δ_{1H} = 1.18-0.87 ppm; δ_{2H} = 2.06 ppm (q); δ_{4H} = 5.54 ppm (m); δ_{7H} = 2.22 ppm (t, d); δ_{8H} = 1.63-1.34 ppm (pentet); δ_{9H} = 1.15-0.87 ppm; δ_{SC₂H₅} = 2.61 ppm (q) and 1.15-0.87 ppm. The small splitting of the signal originating from the terminal -CH₂- group of the propyl group

(7H) was 2.3 Hz. The experiment was repeated, but no ethyl iodide was added to the reaction mixture, which changed the component distribution of the reaction product as shown in Scheme 4, condition II.

(Z)-2-Ethylthio-6,6-dimethyl-2-hepten-4-yne (26). The general method G was followed. From 4.66 g (0.0200 mol) of 3-bromo-2-t-butyl-5-methylthiophene (25) in 50 ml of ether, 38 ml (0.023 mol) of 0.60 M ethereal ethyllithium and 15.6 g (0.100 mol) of ethyl iodide, 3.13 g (86 %) of crude 26 was obtained. Combined vpc-ms analysis (column SE30, 3 %, 100-200°C, 10°/min) showed the following compounds: 27 (10 %, m/e = 154; calc. for C₉H₁₄S = 154) and 26 (90 %, m/e = 182; calc. for C₁₁H₁₈S = 182). See Scheme 4, condition I, and for fragmentation see 2.9, Table 3. Isolation of 26 through distillation was unsuccessful due to vigorous foaming and therefore a pure sample was obtained through preparative tlc (1 mm silica gel, hexane, R_f 0.35-0.16); n_D²¹ 1.5110. Ir: C=C 2220 and 2190 cm⁻¹, C=C 1585 cm⁻¹. Nmr (CCl₄): δ_{1H} = 1.97 ppm (d, 3H); δ_{3H} = 5.34 ppm (q, 1H); δ_{C(CH₃)₃} = 1.25 ppm (s); δ_{SC₂H₅} = 2.83 ppm (q, 2H) and 1.1-1.3 ppm. J_{1H, 3H} = 1.4 Hz. [Found: C 72.50; H 10.00; S 17.52. Calc. for C₁₁H₁₈S (182.33): C 72.46; H 9.95; S 17.59.]

The experiment was repeated, but no ethyl iodide was added to the reaction mixture, which changed the component distribution of the reaction product as shown in Scheme 4, condition II.

(Z)-3-Ethylthio-2,2-dimethyl-3-hepten-5-yne (30) and 5-t-butyl-3-ethyl-2-methylthiophene (31). The general method G was followed. From 28.0 g (0.100 mol) of 5-t-butyl-3-iodo-2-methylthiophene (29) in 200 ml of ether, 200 ml (0.11 mol) of 0.55 M ethereal ethyllithium and 78.0 g (0.500 mol) of ethyl iodide, 16.6 g (91 %) of a crude mixture of 30 and 31 was obtained. Combined vpc-ms analysis (column SE30, 3%, 100-200°C, 10°/min) of the washed and dried reaction mixture showed the presence of the following compounds: 27 (4 %, m/e = 154; calc. for C₉H₁₄S = 154), 31 (46 %, m/e = 182; calc. for C₁₁H₁₈S = 182) and 30 (50 %, m/e = 182; calc. for C₁₁H₁₈S = 182). See Scheme 4, condition I and for fragmentation see 2.9, Table 3.

Also in this experiment, distillation was unsuitable due to foaming. Compound 31 was obtained pure by preparative vpc

(column BDS, 20 %, 100-200°C, 10°/min). Thus, 5.00 g of the crude product gave 1.8 g (33 %) of 31. Nmr (CCl₄): $\delta_{4H} = 6.35$ ppm (s); $\delta_{2CH_3} = 2.23$ ppm (s); $\delta_{C(CH_3)_3} = 1.30$ ppm (s); $\delta_{3C_2H_5} = 2.40$ ppm (q) and 1.13 ppm (t). $J_{CH_2-CH_3} = 7$ Hz. [Found: C 72.2; H 9.88; S 17.6. Calc. for C₁₁H₁₈S (182.33): C 72.46; H 9.95; S 17.59.]

Compound 30 was obtained pure by preparative tlc (1 mm silica gel, hexane, Rf 0.52-0.64). Compound 31 had Rf 0.18-0.36, but was not isolated in this way. Thus, 1.00 g of the crude product gave 0.38 g (35 %) of 30, $n_D^{21} = 1.5149$. Ir: C≡C 2220 and 2040 cm⁻¹, C=C 1580 cm⁻¹. Nmr (CCl₄): $\delta_{C(CH_3)_3} = 1.14$ ppm (s); $\delta_{4H} = 5.75$ ppm (q, 1H); $\delta_{7H} = 1.99$ ppm (d, 3H); $\delta_{SC_2H_5} = 2.98$ ppm (q, 2H) and 1.09-1.33 ppm. $J_{SCH_2-CH_3} = 7.5$ Hz; $J_{4H,7H} = 2.4$ Hz. [Found: C 72.2; H 9.87; S 17.3. Calc. for C₁₁H₁₈S (182.33): C 72.46; H 9.95; S 17.59.]

The experiment was repeated, but no ethyl iodide was added to the reaction mixture, which changed the component distribution as shown in Scheme 4, condition II.

(Z)-2-Ethylthio-3-methyl-2-hexen-4-yne (33). The general method G was followed. From 10.0 g (0.0397 mol) of 3-iodo-2,4,5-trimethylthiophene (32) in 100 ml of ether, 67 ml (0.040 mol) of 0.60 M ethereal ethyllithium and 21.8 g (0.200 mol) of ethyl bromide, 5.50 g of crude product was obtained. Distillation gave 3.12 g (51 %) of 33, b.p._{0.6} 52-54°C. Ir: C≡C 2220 and 2040 cm⁻¹. Nmr (CCl₄): $\delta_{CH_3} = 1.82$ ppm (s, 3H) and 1.97 ppm (bs, 6H); $\delta_{SC_2H_5} = 2.72$ ppm (q, 2H) and 1.21 ppm (t, 3H). $J_{SCH_2-CH_3} = 7$ Hz. [Found: C 70.00; H 9.10; S 20.85. Calc. for C₉H₁₄S (154.28): C 70.07; H 9.15; S 20.78.]

Hex-2-on-4-yne (36). In 600 ml of dry ether, 15.0 g (0.0676 mol) of 2,5-dimethyl-3-iodofuran (34) was dissolved and cooled to -5°C. Butyllithium in hexane/ether (0.072 mol of 1.60 M BuLi in 90 ml of hexane/ether 1:1) was added dropwise at such a rate that the reaction temperature did not exceed -4°C. The reaction mixture was stirred at -5°C for 3 h, and hydrolyzed with an ice-cooled conc. aqueous solution of NH₄Cl. The temperature did not exceed 0°C. To ensure an acidic solution, 0.5 N

HCl was added immediately afterwards. The ether phase was separated and washed with water until neutral reaction. After drying, the ether phase was analyzed by vpc (column BDS, 10 %, 100°C) and found to consist of two components with equal peak area, namely butyl iodide and the title compound. Evaporation left 2.12 g (33 %) of a yellow liquid, which according to vpc analysis consisted of only one component. Recrystallization from pentane at -25°C gave the pure sample. Distillation at 15 mm Hg yielded a fraction at 46-47°C, but as extensive decomposition occurred, recrystallization was preferable. Ir: $\text{C}\equiv\text{C}$ 2230 cm^{-1} , $\text{C}=\text{O}$ 1725 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 2.19$ (bs, 3H); $\delta_{3\text{H}} = 3.07$ (bq, 2H); $\delta_{6\text{H}} = 1.81$ ppm (t, 3H). $J_{3\text{H}, 6\text{H}} = 2.65$ Hz. [Found: m/e 96; C 74.5; H 8.43. Calc. for $\text{C}_6\text{H}_8\text{O}$ (96.13): C 74.97; H 8.39.] It should be pointed out that when the reaction mixture was more concentrated, dimeric and polymeric products predominated.

3,4-Hexadien-2-one (37). This compound was detected in the preparation of hex-2-on-4-yne (36) when the reaction mixture was allowed to be in contact with a basic aqueous solution for more than about 30 sec or when the nmr sample of 36 (in benzene) was treated with one drop of triethylamine. The nmr spectrum was recorded after 5 min. Nmr (benzene): $\delta_{1\text{H}} = 2.02$ ppm (d, 3H); $\delta_{6\text{H}} = 1.52$ ppm (q, 3H); $\delta_{3\text{H}} = 5.60$ ppm (heptet with fine structure, 1H); $\delta_{5\text{H}} = 5.25$ ppm (pentet with fine structure, 1H). $J_{1\text{H}, 3\text{H}} = 0.4$ Hz; $J_{3\text{H}, 6\text{H}} = 3.4$ Hz; $J_{5\text{H}, 6\text{H}} = 7.0$ Hz; $J_{3\text{H}, 5\text{H}} = 6.5$ Hz. Ir: $\text{C}=\text{C}$ 1955 cm^{-1} , $\text{C}=\text{O}$ 1680 cm^{-1} . These data are in agreement with those for similar compounds.⁶⁵ [Found: m/e = 96; Calc. for $\text{C}_6\text{H}_8\text{O}$: m.wt. 96.13.]

(Z)-1-Ethylthio-1-cyclopentadecen-3-yne (42). The general method G was followed. From 2.00 g (6.34 mmol) of 3-bromo[11]-(2,5)-thiophenophane (41) in 25 ml of ether, 8.0 ml (6.4 mmol) of 0.80 M ethereal ethyllithium and 5.0 g (32 mmol) of ethyl iodide, 1.55 g of a crude product was obtained. Combined vpc-ms analysis (column OV1, 3 %, 150-250°C, 15°/min) showed the presence of [11](2,5)-thiophenophane (39) (m/e = 236; calc. for $\text{C}_{15}\text{H}_{24}\text{S}$ = 236) and 42 (m/e = 264; calc. for $\text{C}_{17}\text{H}_{28}\text{S}$ = 264) in the proportions 20:80. The two components were separated and isolated by preparative tlc (silica gel 1 mm, hexane), which gave 0.15 g (10 %) of 39 (Rf 0.48-0.65) and 0.75 g (45 %) of the title compound 42 (Rf 0.10-0.39). Ir: $\text{C}\equiv\text{C}$ 2205 cm^{-1} (weak),

C=C 1575 cm^{-1} . ^1H nmr (CCl_4): $\delta_{2\text{H}} = 5.48$ ppm (bt, 1H); $\delta_{\text{S-CH}_2-} = 2.83$ ppm (q, 2H); $\delta_{\text{alkyl}} = 2.0\text{--}2.5$ ppm (4H) and 1.1–1.7 ppm (21H). $J_{\text{SCH}_2-\text{CH}_3} = 7$ Hz. ^{13}C nmr (acetone, decoupled spectrum): $\delta_{1\text{C}} = 155.7$ ppm; $\delta_{2\text{C}} = 114.9$ ppm; $\delta_{3\text{C}}, \delta_{4\text{C}} = 86.8$ and 105.4 ppm; $\delta_{5\text{C-15C}} = 22.2\text{--}43.7$ ppm; $\delta_{\text{S-CH}_2-} = 43.7$ ppm; $\delta_{-\text{CH}_3} = 22.2$ ppm. [Found: C 76.4; H 10.5; S 11.9. Calc. for $\text{C}_{17}\text{H}_{28}\text{S}$ (264.48): C 77.20; H 10.67; S 12.12.]

Experimental part of Chapter 2.2

Ring-opening of 3-thienyllithium. a) Thienyllithium was prepared from 10.0 g (0.0614 mol) of 3-bromothiophene and 85 ml (0.068 mol) of 0.80 M ethyllithium at -70°C . After 10 min, 20.2 g (0.185 mol) of ethyl bromide was added and the solution was allowed to reach room temperature. After 5 h, the reaction mixture was poured onto solid carbon dioxide in ether. A quantity of 3.8 g (~ 48 %) of an acid mixture was isolated, which according to nmr analysis consisted of 85 mol % 3-thiophene-carboxylic acid, 10 mol % 3-bromo-2-thiophenecarboxylic acid and about 5 mol % of a substance, which is probably (Z)-1-ethylthio-1-buten-3-yne-4-carboxylic acid. Nmr (acetone- d_6): $\delta_{1\text{H}', 2\text{H}} = 7.20$ ppm and 5.65 ppm (d); $\delta_{\text{S-C}_2\text{H}_5} = 2.93$ ppm (q) and 1.33 ppm (t). $J_{1\text{H}, 2\text{H}} = 10$ Hz; $J_{\text{SCH}_2-\text{CH}_3} = 8$ Hz. Ir: C=C 2190 cm^{-1} . The neutral phase (1.1 g) consisted according to vpc analysis (column NPGS, 5 %, 100°C) of three components, viz., thiophene (retention time), 3-ethylthiophene (nmr) and (Z)-1-ethylthio-1-buten-3-yne (43) (nmr). The 3-ethylthiophene¹⁷⁵ (44) could be obtained pure through distillation. B.p._g $40\text{--}45^\circ\text{C}$ (0.18 g, 2.6 %) (lit.¹⁷⁵ b.p. 136°C). Nmr (CCl_4): $\delta_{5\text{H}} = 7.10$ ppm (q, 1H); $\delta_{2\text{H}, 4\text{H}} = 6.82$ ppm (m, 2H); $\delta_{\text{C}_2\text{H}_5} = 2.62$ ppm (q, 2H) and 1.22 ppm (t, 3H). $J_{\text{CH}_2-\text{CH}_3} = 7.2$ Hz; $J_{4\text{H}, 5\text{H}} = 4.8$ Hz; $J_{2\text{H}, 5\text{H}} = 2.8$ Hz. (Cf. Ref. 160.)

b) (Z)-1-Ethylthio-1-buten-3-yne (43). The general method G was followed except that the reaction mixture was hydrolyzed after 5 h. From 5.25 g (0.0250 mol) of 3-iodothiophene, 50 ml (0.028 mol) of 0.55 M ethereal ethyllithium and 8.2 g (0.075

mol) of ethyl bromide, an ethereal phase was obtained having the composition shown in Scheme 5 (vpc: column NPGS, 5 %, 100°C). Evaporation gave 0.75 g of crude product, which was chromatographed on a silica gel column to give a few mg of the title compound. (The starting material was eluted with hexane and addition of up to 10 % of ether gave the enyne.) Ir: $\equiv\text{CH}$ 3300 cm^{-1} , $\text{C}\equiv\text{C}$ 2080 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}}$ = 6.48 ppm (d,d,1H); $\delta_{2\text{H}}$ = 5.38 ppm (d,d,1H); $\delta_{4\text{H}}$ = 3.21 ppm (d,d,1H); $\delta_{\text{SC}_2\text{H}_5}$ = 2.67 ppm (q,2H) and 1.33 ppm (t,3H). $J_{2\text{H},4\text{H}}$ = 2.4 Hz; $J_{1\text{H},4\text{H}}$ = 0.8 Hz; $J_{1\text{H},2\text{H}}$ = 9.8 Hz (cis); $J_{\text{SCH}_2-\text{CH}_3}$ = 7 Hz. [Found: m/e = 112 (for fragmentation see 2.9, Table 3); C 63.84; H 7.05. Calc. for $\text{C}_6\text{H}_8\text{S}$ (112.19): C 64.23; H 7.19.]

By performing the experiment with 3-bromothiophene the result was not changed significantly (see Scheme 5). It was, however, more difficult to isolate the title compound in the presence of 3-bromothiophene, due to similar retention times on the silica gel column.

A slight decrease in the amount of 43 was noticed when 3-thienyllithium was prepared from 3-bromothiophene at -70°C and then allowed to reach room temperature and kept there for 5 h before hydrolysis (see Scheme 5).

3-Selenophenecarboxylic acid.⁴¹ A 10.5 g (0.050 mol) sample of 3-bromoselenophene in 50 ml of dry ether was cooled to -70°C. To this mixture, 100 ml (0.055 mol) of 0.55 N ethereal ethyllithium was added dropwise. After the addition, the reaction mixture was kept at -70°C for 20 min and poured onto solid carbon dioxide in ether. The usual work-up gave 6.72 g (77 %) of 3-selenophenecarboxylic acid, m.p. 146-147°C from water (lit.⁴¹ 145-146°C). When the experiment was performed at -50°C, 5.1 g (58 %) of 3-selenophenecarboxylic acid was isolated.

(Z)-1-Ethylseleno-1-buten-3-yne (47).

a) 3-Bromoselenophene (2.1 g, 0.010 mol) and 10 ml of dry ether were cooled to -70°C, and 20 ml (0.011 mol) of 0.55 N ethereal ethyllithium was added dropwise. After 10 min at -70°C, 3.3 g (0.030 mol) of ethyl bromide was added and the cooling bath was removed. After 5 h at room temperature, the reaction mixture was hydrolyzed with water and dilute HCl and worked-up

as described in the general method G. Vpc analysis (column BDS, 10 %, 120°C), showed 50 % of selenophene and 50 % of the title compound. Evaporation of the ether and the selenophene left 0.80 g of crude product (50 % yield). The nmr spectrum showed no impurities. Column chromatography (silica gel, pentane in ether 95:5) gave 0.60 g (38 %) of pure title compound. Ir: $\equiv\text{CH}$ 3300 cm^{-1} , $\text{C}\equiv\text{C}$ 2080 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 6.89$ ppm (d,d,1H); $\delta_{2\text{H}} = 5.84$ ppm (d,d,1H); $\delta_{4\text{H}} = 3.25$ ppm (d,d,1H); $\delta_{\text{SC}_2\text{H}_5} = 1.43$ ppm (t,3H) and 2.76 ppm (q,2H). $J_{2\text{H},4\text{H}} = 2.3$ Hz; $J_{1\text{H},4\text{H}} = 0.8$ Hz; $J_{1\text{H},2\text{H}} = 9.7$ Hz (cis); $J_{\text{SCH}_2-\text{CH}_3} = 7.2$ Hz. [Found: m/e 160 (^{80}Se). For fragmentation see 2.9, Table 3. C 45.27; H 5.08; Se 49.67. Calc. for $\text{C}_6\text{H}_8\text{Se}$ (159.09): C 45.30; H 5.07; Se 49.63.]

b) A higher yield was obtained when the general method G was followed with the same amounts as in the preceding experiment. The vpc analysis (column as above) of the ethereal phase revealed 70 % of the title compound and 27 % of selenophene. A small peak (3 %) due to starting material was also present. Distillation of the ether at normal pressure gave 1.6 g of crude product with the same composition as the ethereal phase.

The reaction between 3-bromofuran and butyllithium. The general method G was followed. From 14.7 g (0.100 mol) of 3-bromofuran in 600 ml of ether, 63 ml (0.10 mol) of 1.60 M ethereal butyllithium* and 41.1 g (0.300 mol) of butyl bromide, 3.0 g of a brown solid product was obtained by suction of the hydrolyzed reaction mixture. (The reaction mixture turned brown upon hydrolysis.) Ir showed no acetylenic absorptions. The solid could not be dissolved in any solvent attempted. The reaction was repeated at 0°, -10°C and -20°C with the same results.

Experimental part of Chapter 2.3

(Z)-2-Ethylthio-5-phenyl-2-penten-4-yne (51). The general method G was followed. From 5.06 g (0.0200 mol) of 3-bromo-5-methyl-2-phenylthiophene (48) in 50 ml of ether, 28 ml (0.021 mol) of 0.76 M ethereal ethyllithium and 10.9 g (0.100 mol) of ethyl bromide, 3.23 g of crude product was obtained. Combined

* A white precipitate was formed when the butyllithium solution was added.

vpc-ms analysis (column OV 17, 3 %, 100-230°C, 12°/min) of the washed and dried ethereal reaction mixture showed three components, namely 49 (m/e = 174; calc. for $C_{11}H_{10}S$ = 174), 50 (m/e = 202; calc. for $C_{13}H_{14}S$ = 202), and 51 (m/e = 202; calc. for $C_{13}H_{14}S$ = 202). See Scheme 6 and for fragmentation see 2.9, Table 3. After distillation, 1.9 g (47 %) of the title compound was obtained, b.p._{5.10-3} 105-110°C. Ir: $C\equiv C$ 2190 cm^{-1} . Nmr (CCl_4): δ_{1H} = 2.00 ppm (d,3H); δ_{3H} = 5.57 ppm (q,1H); $\delta_{C_6H_5}$ = 7.1-7.6 ppm (m,5H); $\delta_{SC_2H_5}$ = 2.80 ppm (q,2H) and 1.23 ppm (t, 3H). $J_{1H,3H}$ = 1.4 Hz; $J_{SCH_2-CH_3}$ = 7.0 Hz. [Found: C 76.9; H 7.01; S 15.7. Calc. for $C_{13}H_{14}S$ (202.32): C 77.18; H 6.98; S 15.85.]

(Z)-1-Ethylthio-1-phenyl-1-penten-3-yne (58). The general

method G was followed. From 5.06 g (0.0200 mol) of 3-bromo-2-methyl-5-phenylthiophene (56) in 50 ml of ether, 30 ml (0.021 mol) of 0.70 M ethereal ethyllithium and 7.80 g (0.0500 mol) of ethyl iodide, 3.52 g of a crude product was obtained. Combined vpc-ms analysis (column OV 17, 3 %, 200-290°C, 12°/min) showed the presence of four compounds, namely 49 (m/e = 174; calc. for $C_{11}H_{10}S$ = 174), 57 (m/e = 202; calc. for $C_{13}H_{14}S$ = 202), 58 (m/e = 202; calc. for $C_{13}H_{14}S$ = 202) and (Z)-1-ethylthio-1-phenyl-1-hepten-3-yne (m/e = 230; calc. for $C_{15}H_{18}S$ = 230). See Scheme 6 and for fragmentation see 2.9, Table 3. Tlc (1 mm silica gel, hexane) of 1.50 g of the crude product gave 0.94 g (55 %) of the title compound (Rf 0.2-0.4). Ir: $C\equiv C$ 2215 and 2040 cm^{-1} . Nmr (CCl_4): δ_{2H} = 5.73 ppm (q,1H); δ_{5H} = 2.05 ppm (d,3H); $\delta_{C_6H_5}$ = 7.17-7.60 ppm (m,5H); $\delta_{SC_2H_5}$ = 2.50 ppm (q,2H) and 1.08 ppm (t,3H). $J_{2H,5H}$ = 2.40 Hz; $J_{SCH_2-CH_3}$ = 7.0 Hz. [Found: C 77.10; H 7.01; S 15.85. Calc. for $C_{13}H_{14}S$ (202.32): C 77.18; H 6.98; S 15.85.]

(Z)-2-Ethylthio-3-phenyl-2-penten-4-yne (55). The general method G was followed. From 2.00 g (6.37 mmol) of 3-iodo-2,5-dimethyl-4-phenylthiophene (52) in 30 ml of ether, 14 ml (6.40 mmol) of 0.46 M ethereal ethyllithium and 3.27 g (30.0 mmol) of ethyl bromide, 0.90 g of a crude product was obtained. Combined vpc-ms analysis (column OV 1, 3 %, 100-290°C, 10°/min) of the washed and dried reaction mixture showed the presence of three

compounds, namely 53 ($m/e = 188$; calc. for $C_{12}H_{12}S = 188$), 54 ($m/e = 216$; calc. for $C_{14}H_{16}S = 216$), and 55 ($m/e = 216$; calc. for $C_{14}H_{16}S = 216$). See Scheme 6. Tlc (1 mm silica gel, hexane) gave two fractions: Z 1 (0.23 g, Rf 0.30-0.54), which according to nmr and vpc analysis consisted of 53 and 54, Z 2 (0.16 g, 12 %, Rf 0.12-0.05), which was the crystalline title compound. Recrystallization from hexane at $-25^{\circ}C$ gave 55, m.p. $58-60^{\circ}C$. Ir: $C\equiv C$ 2110 and 2040 cm^{-1} . Nmr (CCl_4): $\delta_{1H,6H} = 2.02\text{ ppm}$ (bs, 6H); $\delta_{C_6H_5} = 7.20\text{ ppm}$ (m, 5H); $\delta_{SC_2H_5} = 2.83\text{ ppm}$ (q, 2H) and 1.32 ppm (t, 3H). $J_{SCH_2-CH_3} = 7\text{ Hz}$. [Found: C 77.79; H 7.46; S 14.77. Calc. for $C_{14}H_{16}S$ (216.35): C 77.72; H 7.45; S 14.82.]

(Z)-2-Methylthio-5-phenyl-2-penten-4-yne (60). To 1.50 g (5.00 mmol) of 3-iodo-5-methyl-2-phenylthiophene (59) in 25 ml of ether, 5.0 ml (5.0 mmol) of 1.0 M phenyllithium was added (with a syringe) at room temperature and in a glove-box supplied with dry (2 rel %) oxygen-free nitrogen. After 4 h, 0.63 g (5.0 mmol) of dimethyl sulphate in 10 ml of ether was added and the reaction mixture was hydrolyzed with 10 ml of conc. ammonium hydroxide solution after another hour. The mixture was washed with 2 N HCl and water to neutral reaction and dried. After evaporation of the ether and lower boiling substances (e.g. iodobenzene), 0.90 g of crude product remained, which was chromatographed (tlc, 1 mm silica gel, hexane) to give 0.65 g (69 %) of the title compound. Ir: $C\equiv C$ 2185 cm^{-1} . Nmr (CCl_4): $\delta_{1H} = 2.10\text{ ppm}$ (d, 3H); $\delta_{3H} = 5.54\text{ ppm}$ (q, 1H); $\delta_{C_6H_5} = 7.1-7.5\text{ ppm}$ (m, 5H); $\delta_{SCH_3} = 2.37\text{ ppm}$ (s, 3H). $J_{1H,3H} = 1.4\text{ Hz}$. [Found: C 76.44; H 6.39; S 17.18. Calc. for $C_{12}H_{12}S$ (188.29): C 76.55; H 6.42; S 17.03.]

(Z)-1-Methylthio-1-phenyl-1-penten-3-yne (62). This compound was prepared with the same method and in the same scale as the preceding experiment from 3-iodo-2-methyl-5-phenylthiophene (61). The crude product (0.60 g) was purified by tlc (1 mm silica gel, hexane), giving 0.47 g (50 %) of the title compound. Ir: $C\equiv C$ 2220 cm^{-1} . Nmr (CCl_4): $\delta_{2H} = 5.65\text{ ppm}$ (q, 1H); $\delta_{5H} = 2.05\text{ ppm}$ (d, 3H); $\delta_{C_6H_5} = 7.1-7.6\text{ ppm}$ (m, 5H); $\delta_{SCH_3} = 2.03\text{ ppm}$ (s, 3H). $J_{2H,5H} = 2.4\text{ Hz}$. [Found: C 76.50; H 6.40; S 17.13. Calc. for $C_{12}H_{12}S$ (188.29): C 76.55; H 6.42; S 17.03.]

(Z)-2-Methylthio-3-phenyl-2-hexen-4-yne (63). As in the preceding experiment, compound 63 was prepared from 3-iodo-2,5-dimethyl-4-phenylthiophene (52). The crude product (0.85 g) was purified as above, which gave the title compound, 0.64 g (63 %), m.p. 84-86°C. Ir: $\text{C}\equiv\text{C}$ 2200 cm^{-1} . Nmr (CCl_4): $\delta_{\text{H},6\text{H}} = 2.00$ ppm (bs, 6H); $\delta_{\text{C}_6\text{H}_5} = 7.17$ ppm (s, 5H); $\delta_{\text{SCH}_3} = 2.32$ ppm (s, 3H). [Found: C 77.24; H 7.01; S 15.80. Calc. for $\text{C}_{13}\text{H}_{14}\text{S}$ (202.32): C 77.18; H 6.98; S 15.85.]

Experimental part of Chapter 2.4

2-Methoxy-5-methyl-3-thiophenecarboxylic acid⁴⁸ (66). A solution of 2.07 g (0.0100 mol) of 3-bromo-2-methoxy-5-methylthiophene (64) in 30 ml of ether was treated with 17 ml (0.010 mol) of 0.60 M ethereal ethyllithium and 5.45 g (0.0500 mol) of ethyl bromide according to the general method G, except that the reaction mixture was poured onto solid carbon dioxide in ether after 4 h. The usual work-up gave 1.2 g (70 %) of the title compound, m.p. $\sim 145^\circ\text{C}$, which after recrystallization from water had m.p. 146-148°C (lit.⁴⁸ m.p. 147-148°C, 50 %). Nmr (acetone- d_6): $\delta_{4\text{H}} = 6.75$ ppm (q, 1H); $\delta_{5\text{CH}_3} = 2.32$ ppm (d, 3H); $\delta_{\text{OCH}_3} = 3.98$ ppm (s, 3H). $J_{4\text{H},5\text{CH}_3} = 1.3$ Hz. No signs of acetylenes were observed (ir) in the neutral phase, which amounted to 0.1 g of (mainly) 2-methoxy-5-methylthiophene (nmr).

2-Chloro-5-methyl-3-thiophenecarboxylic acid (67). A solution of 1.0 g (4.7 mmol) of 3-bromo-2-chloro-5-methylthiophene (65) in 25 ml of ether was treated with 10.0 ml (4.7 mmol) of 0.47 M ethereal ethyllithium and 2.2 g (20 mmol) of ethyl bromide according to the general method G, except that the reaction mixture was poured onto solid carbon dioxide in ether after 4 h. Thus, 0.3 g (36 %) of the title compound was obtained after the usual work-up. The acid was recrystallized from ethanol:water, m.p. 165-168°C. Ir: $\text{C}=\text{O}$ 1680 cm^{-1} . Nmr (CDCl_3): $\delta_{4\text{H}} = 7.06$ ppm (q, 1H); $\delta_{5\text{CH}_3} = 2.40$ ppm (d, 3H); $\delta_{\text{COOH}} = 11.25$ ppm (s, 1H). $J_{4\text{H},5\text{CH}_3} = 1.1$ Hz. [Found: C 40.76; H 2.80; S 18.19. Calc. for $\text{C}_6\text{H}_5\text{ClO}_2\text{S}$ (176.62): C 40.80; H 2.85; S 18.15.]

The neutral ethereal phases contained 2-chloro-5-methylthio-

phene and 2-chloro-3-ethyl-5-methylthiophene (68) in the proportions 4:6 according to vpc analysis (OV 17, 3 %, 100-200°C, 15°/min) and comparison of the retention times with those of authentic samples. Evaporation of the solvent gave 0.4 g of an oil, which showed no signs of acetylenes (ir).

2-Chloro-3-ethyl-5-methylthiophene (68). A solution of 10.0 g (0.0473 mol) of 3-bromo-2-chloro-5-methylthiophene (65) in 100 ml of ether was treated with 51 ml (0.048 mol) of 0.94 M ethereal ethyllithium and 16.4 g (0.150 mol) of ethyl bromide, according to the general method G, except that the reaction mixture was stirred at room temperature for 24 h before hydrolysis. Thus, 5.32 g of a crude product remained after work-up and evaporation of the solvent. The title compound was obtained through distillation, b.p.₁₆ 83-85°C, 3.9 g (51 %). Nmr (CCl₄): $\delta_{4H} = 6.37$ ppm (q, 1H); $\delta_{5CH_3} = 2.32$ ppm (d); $\delta_{3C_2H_5} = 2.50$ ppm (q) and 1.13 ppm (t, 3H). $J_{4H, 5CH_3} = 1.1$ Hz; $J_{CH_2-CH_3} = 7.0$ Hz. [Found: C 51.7; H 5.51. Calc. for C₇H₉ClS (160.67): C 52.33; H 5.65.] No traces of acetylenes were found in the crude product (ir).

2,5-Dichloro-3-methylthiophene^{77a,b} (70).

a) The general method G was followed, except that the reaction mixture was hydrolyzed after 2 h. From 2.79 g (0.0100 mol) of 2,5-dichloro-3-iodothiophene (69) in 10 ml of ether, 17 ml (0.010 mol) of 0.60 M ethereal ethyllithium and 4.3 g (0.030 mol) of methyl iodide, 1.0 g (60 %) of crude 70 was obtained. Vpc (column NPGS, 5 %, 90-180°C, 13°/min) and nmr showed the presence of only one component; b.p.₁₄ 71-72°C, 0.9 g (55 %), $n_D^{20} = 1.5540$ (lit.^{78a} b.p.₁₁ 65°C, $n_D^{20} = 1.5560$). Ir showed no signs of acetylenes. Nmr (CCl₄): $\delta_{3CH_3} = 2.08$ ppm (s, 3H); $\delta_{4H} = 6.45$ ppm (s, 1H).

b) To 11 ml (0.011 mol) of 1.0 M ethereal phenyllithium, 2.79 g (0.0100 mol) of 69 was added. After 2 h at room temperature, a solution of 1.9 g (0.015 mol) of DMS in 25 ml of ether was added. One hour later the excess DMS was destroyed by adding 25 ml of conc. ammonium hydroxide solution to the reaction mixture. The ethereal layer was washed with water, 2 N HCl and water to neutral reaction. Vpc (OV 1, 3 %, 70-220°C, 10°/min) showed < 10 % of toluene, 0.5 % of 2,5-dichlorothiophene, 42 % of iodo-

benzene, and 40 % of 70, upon comparison of the retention times with those of authentic compounds. Ir showed no signs of acetylenes in the evaporated crude product.

Attempted metalation of 2-methoxy-5-methylselenophene (143).

To a solution of 0.46 g (2.6 mmol) of 2-methoxy-5-methylselenophene¹⁵³ (143), 6.0 ml (3.0 mmol) of 0.50 M ethereal ethyllithium was added at room temperature. The yellow solution darkened rapidly and was black after 1 min. The reaction mixture was poured onto solid carbon dioxide in ether after 15 min, but no selenophenecarboxylic acid could be isolated. Instead elemental selenium precipitated from the acidified alkaline extract. The neutral phase contained 0.2 g of the starting material.

2,5-Dichloro-3-selenienyl 1,4-dichloro-1-buten-3-yn-1-yl selenide (72). To 6.52 g (0.0200 mol) of 2,5-dichloro-3-iodoselenophene (71), 17 ml (0.010 mol) of 0.60 M ethereal ethyllithium was added dropwise at -70°C. After 5 min, the reaction mixture was poured onto solid carbon dioxide in ether. No carboxylic acid could be isolated from the alkaline aqueous extracts upon acidification with 2 N HCl. From the neutral, dried ethereal phase, 3.90 g of a brown oil remained after evaporation of the solvent. (Upon standing at room temperature the oil darkened and solidified.) Mass spectrum of the oil (direct inlet): $m/e = 398$; calc. for $C_8H_2Cl_4^{80}Se_2 = 398$. The isotopic pattern of the M^+ ion is discussed in 2.9. 1H nmr (CCl_4): singlets at $\delta = 6.96$ ppm and $\delta = 6.10$ ppm, integrals 1:1. Absorptions from the starting material and 2,5-dichlorothiophene were also present, and the yield of 72 based on the nmr data and the weight of the crude product was ~ 60 %. Ir: $C\equiv C$ 2190 and 2265 cm^{-1} , $C=C$ 1550 cm^{-1} . ^{77}Se nmr data are discussed in 2.4. Attempts to isolate 72 by preparative tlc, using a number of eluents were unsuccessful, mainly due to instability of the compound. The experiment was repeated several times, which gave mixtures, as mentioned above, containing 50-65 % of 72.

2,5-Dichloro-3-selenophenecarboxylic acid (75). Lithium-diisopropylamide was prepared from 1.1 g (0.011 mol) of diisopropylamine in 20 ml of ether and 18 ml (0.011 mol) of 0.60 M ethereal ethyllithium. This solution was added dropwise to 2.00 g (0.0100 mol) of 2,5-dichloroselenophene (74) in 30 ml of ether

at -70°C . After 2 h, the reaction mixture was poured onto solid carbon dioxide in ether. Upon acidification of the alkaline aqueous extracts with 2 N HCl, 1.9 g (78 %) of the title compound was isolated, m.p. $\sim 145^{\circ}\text{C}$. Recrystallization from ethanol:water gave the pure acid, m.p. $151-153^{\circ}\text{C}$. Ir: $\text{C}=\text{O}$ 1690 cm^{-1} . Nmr ($\text{DMSO}-d_6$): $\delta_{4\text{H}} = 7.42\text{ ppm}$ (s). [Found: C 24.70; H 0.91; Se 32.31. Calc. for $\text{C}_5\text{H}_2\text{Cl}_2\text{O}_2\text{Se}$ (243.93): C 24.62; H 0.83; Se 32.37.]

(Z)-1-Methoxy-1-methylthio-1-penten-3-yne (78). To 1.82 g (8.80 mmol) of 3-bromo-5-methoxy-2-methylthiophene (76) in 50 ml of ether, 13 ml (9.1 mmol) of 0.70 M ethereal ethyllithium was added, followed by 4.9 g (45 mmol) of ethyl bromide. A white precipitate was formed after the addition of the ethyllithium. On the addition of 2.0 ml of dry HMPA, the precipitate dissolved with heat evolution. Samples of the reaction mixture were withdrawn with a pipette, hydrolyzed and analyzed by vpc (OV 17, 3 %, $100-210^{\circ}\text{C}$, $15^{\circ}/\text{min}$). It appeared that the ring-opening was complete in less than 2 h; 86 % of 78 and 14 % of a compound with longer retention time were found. After 4 h, the reaction mixture was hydrolyzed with water and the ethereal layer was separated, washed with 2 N HCl, water and dried. Preparative tlc (1 mm silica gel, hexane:ether 9:1) of the evaporated crude product (1.20 g) gave 0.45 g (33 %) of the title compound. Ir: $\text{C}\equiv\text{C}$ 2210 and 2040 cm^{-1} . Nmr (CCl_4): $\delta_{2\text{H}} = 4.72\text{ ppm}$ (q, 1H); $\delta_{5\text{H}} = 1.95\text{ ppm}$ (d, 3H); $\delta_{\text{OCH}_3} = 3.67\text{ ppm}$ (s, 3H); $\delta_{\text{SC}_2\text{H}_5} = 2.75\text{ ppm}$ (q, 2H) and 1.25 ppm (t, 3H). $J_{2\text{H}, 5\text{H}} = 2.2\text{ Hz}$; $J_{\text{SCH}_2-\text{CH}_3} = 7.0\text{ Hz}$. [Found: C 61.39; H 7.63; S 20.35. Calc. for $\text{C}_8\text{H}_{12}\text{OS}$ (156.25): C 61.50; H 7.74; S 20.52.]

When the experiment was performed as described above but without HMPA, the peak of the title compound increased in height even after 4 h, as was evident from vpc analyses (the same column as above) of hydrolyzed samples from the reaction mixture. The peak originating from 2-methoxy-5-methylthiophene decreased simultaneously.

1-Ethylthio-1,3-pentadiyne⁸¹ (79). The general method G was followed. From 0.50 g (2.4 mmol) of 3-bromo-5-chloro-2-methylthiophene (77) in 7 ml of ether, 3.2 ml (2.4 mmol) of 0.75 M ethereal ethyllithium and 1.1 g (10 mmol) of ethyl bromide,

0.3 g of a crude product was obtained. (A yellow precipitate was formed in the reaction mixture.) Ir: $\text{C}\equiv\text{C}$ 2205 cm^{-1} . Combined vpc-ms analysis (column BDS, 10 %, 100-200°C, 10°/min) of the washed and dried ethereal reaction mixture: 42 % of 2-chloro-5-methylthiophene, (m/e = 132; calc. for $\text{C}_5\text{H}_5^{35}\text{ClS}$ = 132); 21 % of the starting material (the same retention time as an authentic sample) and 37 % of the title compound, m/e = 124; calc. for $\text{C}_7\text{H}_8\text{S}$ = 124. Nmr (CCl_4): besides absorptions from 77 and 2-chloro-5-methylthiophene there were absorptions originating from 79: δ_{CH_3} = 1.95 ppm (s) (lit.⁸¹ δ_{CH_3} = 1.97±0.02 ppm) and $\delta_{\text{SC}_2\text{H}_5}$ = 2.70 ppm (q, 2H) and 1.40 ppm (t, 3H). Uv (cyclohexane) of a purified sample (tlc: 1 mm silica gel, hexane) λ_{max} (nm): 239.5, 255 (sh), 268, 286. Lit.⁸¹ (no solvent notation) 242, 253, 268, 284.

Reaction between ethyllithium and 3-bromo-5-methyl-2-methylthiothiophene (80).

a) (Z)-2-Ethylthio-5-methylthio-2-penten-4-yne (81). The general method G was followed. From 2.23 g (0.0100 mol) of 3-bromo-5-methyl-2-methylthiothiophene^{82a} (80) in 50 ml of ether, 20 ml (0.012 mol) of 0.60 M ethereal ethyllithium and 3.3 g (0.030 mol) of ethyl bromide, 1.47 g of a crude product was obtained. Combined vpc-ms analysis (column BDS, 10%, 130-190°C, 16°/min) on the washed and dried ethereal reaction mixture showed 5 components (in the order of increasing retention times): 2-methyl-5-methylthiothiophene (m/e = 144; calc. for $\text{C}_6\text{H}_8\text{S}_2$ = 144), 84 (m/e = 126; calc. for $\text{C}_7\text{H}_{10}\text{S}$ = 126), 82 (m/e = 172; calc. for $\text{C}_8\text{H}_{12}\text{S}_2$ = 172), 81 (m/e = 172; calc. for $\text{C}_8\text{H}_{12}\text{S}_2$ = 172) and 83 (m/e = 190; calc. for $\text{C}_7\text{H}_{10}\text{S}_3$ = 190). See Scheme 8 and for fragmentations see 2.9, Table 3. Compound 83 was identified by comparison of its mass spectral data and its retention time with those of an authentic sample. Ir of the crude product: $\equiv\text{CH}$ 3280 cm^{-1} , $\text{C}\equiv\text{C}$ 2138 and 2085 cm^{-1} . An enriched sample of 81 was obtained in the following way: 1) Column chromatography (Al_2O_3 : hexane) was performed on the crude product. The acetylenes are eluted first. 2) The eluate from 1) was evacuated (1 mm Hg) for 2 h. Most of the lower boiling acetylene was removed. 3) Tlc (1 mm silica gel, hexane:ether 9:1) was carried out on the residue from 2). Nmr (CCl_4): $\delta_{1\text{H}}$ = 2.01 ppm (d); $\delta_{3\text{H}}$ = 5.43 ppm (q,

1H); $\delta_{\text{SCH}_3} = 2.40$ ppm (s, 3H); $\delta_{\text{SC}_2\text{H}_5} = 2.85$ ppm (q, 2H) and 1.28 ppm (t, 3H). $J_{1\text{H}, 3\text{H}} = 1.4$ Hz; $J_{\text{CH}_2-\text{CH}_3} = 7$ Hz.

b) (Z)-2-Ethylthio-2-penten-4-yne (84). The general method G was followed. From 2.23 g (0.0100 mol) of 80, 37 ml (0.022 mol) of 0.60 M ethereal ethyllithium and 3.3 g (0.030 mol) of ethyl bromide, 1.0 g of a crude product was obtained. The washed and dried ethereal reaction mixture had the composition presented in Scheme 8. Distillation of the crude product gave a few drops of almost pure 84, b.p.₁₂ 80-90°C. Nmr (CCl_4): $\delta_{1\text{H}} = 2.06$ ppm (d, d, 3H); $\delta_{3\text{H}} = 5.33$ ppm (m); $\delta_{5\text{H}} = 3.08$ ppm (d, d); $\delta_{\text{SC}_2\text{H}_5} = 2.83$ ppm (q) and 1.28 ppm (t, 3H). $J_{3\text{H}, 5\text{H}} = 2.5$ Hz; $J_{1\text{H}, 3\text{H}} = 1.4$ Hz; $J_{1\text{H}, 5\text{H}} = 0.6$ Hz; $J_{\text{SCH}_2-\text{CH}_3} = 7.3$ Hz.

c) The reaction was repeated as in a) but the reagents were mixed at -70°C, after which the temperature was allowed to rise to +21°C. After 4 h at this temperature, the reaction mixture was hydrolyzed and worked-up as in the general method G, which gave 1.1 g of a crude product. The washed and dried ethereal reaction mixture had the composition presented in Scheme 8.

(Z)-2-Ethylseleno-5-methylthio-2-penten-4-yne (86). The general method G was followed. From 3.53 g (0.0131 mol) of 3-bromo-5-methyl-2-methylthioselenophene (85) in 80 ml of ether, 20 ml (0.014 mol) of 0.70 M ethereal ethyllithium and 9.8 g (0.090 mol) of ethyl bromide, 2.50 g of a crude product was obtained. Combined vpc-ms analysis (column BDS, 10 %, 130-190°C, 15°/min) of the washed and dried ethereal reaction mixture showed six components, of which the two most abundant ones were 87 (10 %, m/e = 174; calc. for $\text{C}_7\text{H}_{10}^{80}\text{Se} = 174$) and 86 (80 %, m/e = 220; calc. for $\text{C}_8\text{H}_{12}\text{S}^{80}\text{Se} = 220$). For fragmentation see 2.9, Table 3. Ir: $\text{C}\equiv\text{CH}$ 3280 cm^{-1} , $\text{C}\equiv\text{C}$ 2100 and 2140 cm^{-1} . Distillation of the crude product gave 1.26 g (44 %) of the title compound, b.p.₂₋₁₀₋₂ 74-77°C. Ir: $\text{C}\equiv\text{C}$ 2140 cm^{-1} , $\text{C}=\text{C}$ 1570 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 2.13$ ppm (d, 3H); $\delta_{3\text{H}} = 5.70$ ppm (q, 1H); $\delta_{\text{SCH}_3} = 2.40$ ppm (s, 3H); $\delta_{\text{SeC}_2\text{H}_5} = 2.80$ ppm (q, 2H) and 1.40 ppm (t, 3H). $J_{1\text{H}, 3\text{H}} = 1.4$ Hz; $J_{\text{SeCH}_2-\text{CH}_3} = 7.2$ Hz. [Found: C 43.70; H 5.41; S 14.68; Se 36.20. Calc. for $\text{C}_8\text{H}_{12}\text{SSe}$ (219.21): C 43.83; H 5.52; S 14.63; Se 36.02.]

(Z)-1-Ethylthio-1-methylthio-1-penten-3-yne (89). The general method G was followed. From 10.0 g (0.0448 mol) of 3-bromo-2-methyl-5-methylthiophene (88) in 150 ml of ether, 75 ml (0.045 mol) of 0.60 M ethyllithium and 23.4 g (0.150 mol) of ethyl iodide, 7.5 g of a crude product was obtained, which according to combined vpc-mass spectrometry (column BDS, 10 %, 130-190°C, 16°/min) showed three components (in order of increasing retention time): m/e = 200, unidentified (5 %), 89 (70 %, m/e = 172; calc. for $C_8H_{12}S_2$ = 172) and 90 (25 %, m/e = 200; calc. for $C_{10}H_{16}S_2$ = 200). For fragmentation see 2.9, Table 3. The crude product was distilled at 91-94°/1.2 mm Hg, and the title compound was obtained pure through preparative tlc (1 mm silica gel; hexane:ether, 10:1). Ir: $C\equiv C$ 2205 cm^{-1} , $C=C$ 1540 cm^{-1} . Nmr (CCl_4): δ_{2H} = 5.58 ppm (q, 1H); δ_{5H} = 2.00 ppm (d, 3H); δ_{SCH_3} = 2.28 ppm (s, 3H); $\delta_{SC_2H_5}$ = 2.86 ppm (q, 2H) and 1.28 ppm (t, 3H). $J_{2H,5H}$ = 2.4 Hz; $J_{SCH_2-CH_3}$ = 7.0 Hz. [Found: C 55.7; H 7.04; S 36.9. Calc. for $C_8H_{12}S_2$ (172.31): C 55.76; H 7.02; S 37.22.]

Upon preparative vpc (column BDS, 20 %, 190°C) compound 89 isomerized to a mixture of what were probably the Z and E isomers, since all absorptions in the nmr spectrum were doubled, except the methyl triplet of the S-ethyl group.

(Z)-1-Ethylseleno-1-methylthio-1-penten-3-yne (93). The general method G was followed. From 2.70 g (0.0100 mol) of 3-bromo-2-methyl-5-methylthioselenophene (92) in 50 ml of ether, 16 ml (0.011 mol) of 0.70 M ethereal ethyllithium and 7.6 g (0.070 mol) of ethyl bromide, 1.85 g (84 %) of a crude product was obtained, which according to vpc (column OV 17, 5 %, 170°C) consisted to 95 % of the title compound. Distillation yielded 1.2 g (55 %) of pure 93, b.p. 66-67°/5 x 10⁻³ mm Hg. Ir: $C\equiv C$ 2205 cm^{-1} , $C=C$ 1530 cm^{-1} . Nmr (CCl_4): δ_{2H} = 5.68 ppm (q, 1H); δ_{5H} = 1.97 ppm (d, 3H); δ_{SCH_3} = 2.28 ppm (s, 3H); $\delta_{SeC_2H_5}$ = 2.88 ppm (q, 2H) and 1.43 ppm (t, 3H). $J_{2H,5H}$ = 2.4 Hz; $J_{SeCH_2-CH_3}$ = 7.0 Hz. Mass spectrum: found m/e = 220; calc. for $C_8H_{12}S^{80}Se$ = 220. For fragmentation see 2.9, Table 3. [Found: C 43.78; H 5.52; S 14.58; Se 36.21. Calc. for $C_8H_{12}SSe$ (219.21): C 43.83; H 5.52; S 14.63; Se 36.02.]

Experimental part of Chapter 2.5

The stability of 2-N,N-dimethylaminomethyl-5-methyl-3-thienyllithium. In an nmr tube, 0.117 g (0.500 mmol) of 3-bromo-5,N,N-trimethyl-2-thenylamine (94) was introduced. The tube was sealed with a plastic cap and cooled to -70°C whereupon 0.50 ml of 1.0 M ethereal ethyllithium was injected through the cap by a syringe and the tube was sealed off with a glassblower's torch. The vinyl region was scanned every two hours during 12 h, but no traces of vinylic protons were observed.

5,N,N-Trimethyl-2-thenylamine.¹⁸² The general method G was followed. From 2.34 g (0.0100 mol) of 3-bromo-5,N,N-trimethyl-2-thenylamine (94) in 30 ml of ether, 13 ml (0.010 mol) of 0.80 M ethereal ethyllithium and 5.45 g (0.0500 mol) of ethyl bromide, 1.40 g (90 %) of the crude title compound was obtained after evaporation of the solvent. Vpc (column OV 17, 3 %, $100-250^{\circ}\text{C}$, $20^{\circ}/\text{min}$) showed only one component. Ir: no acetylenic absorptions. Distillation gave the pure title compound, b.p.₁₂ $80-81^{\circ}\text{C}$, $n_{\text{D}}^{20} = 1.5170$. (Lit.¹⁸² b.p.₁₅ $83-84^{\circ}\text{C}$, $n_{\text{D}}^{20} = 1.5150$.) Nmr (CCl_4): $\delta_{3\text{H}} = 6.53$ ppm (bd); $\delta_{4\text{H}} = 6.42$ ppm (d,q); $\delta_{5\text{CH}_3} = 2.43$ ppm (bs,3H); $\delta_{-\text{CH}_2-} = 3.48$ ppm (s,2H); $\delta_{\text{NCH}_3} = 2.20$ ppm (s,6H). $J_{3\text{H},4\text{H}} = 3.2$ Hz; $J_{4\text{H},5\text{CH}_3} = 1.0$ Hz.

(Z)-2-Ethylthio-1-N,N-dimethylamino-2-hexen-4-yne (96).

The general method G was followed. From 10.0 g (0.0427 mol) of 3-bromo-2,N,N-trimethyl-5-thenylamine (95) in 75 ml of ether, 75 ml (0.045 mol) of 0.60 M ethereal ethyllithium and 16.4 g (0.150 mol) of ethyl bromide, 7.6 g of a crude product was obtained. The title compound was obtained pure by distillation, b.p._{0.6} $76-80^{\circ}\text{C}$, 3.8 g (49 %). (Extensive decomposition took place during the distillation.) Ir: $\text{C}\equiv\text{C}$ 2220 cm^{-1} . Nmr (CCl_4): $\delta_{1\text{H}} = 2.97$ ppm (bs,2H); $\delta_{3\text{H}} = 5.53$ ppm (m,1H); $\delta_{6\text{H}} = 1.98$ ppm (d,3H); $\delta_{\text{NCH}_3} = 2.17$ ppm (s,6H); $\delta_{\text{SC}_2\text{H}_5} = 2.97$ ppm (q,2H) and 1.25 ppm (t,3H). $J_{3\text{H},6\text{H}} = 2.4$ Hz; $J_{\text{SCH}_2-\text{CH}_3} = 7.2$ Hz. [Found: C 65.44; H 9.29; S 17.39. Calc. for $\text{C}_{10}\text{H}_{17}\text{NS}$ (183.32): C 65.52; H 9.35; S 17.49.]

Experimental part of Chapter 2.6

3-Carboxy-5-methyl-2-thienylacetic acid (97).

a) To 165 ml (0.104 mol) of 0.63 M ethereal ethyllithium, 11.6 g (0.100 mol) of TMEDA was added, and ten minutes later 11.2 g (0.100 mol) of 2,5-dimethylthiophene all at once (yellow precipitate). After 2 h reflux the reaction mixture was poured onto solid carbon dioxide in ether. The mixture was acidified with 5 N HCl and the aqueous phase was extracted with ether. The combined ether phases were then extracted with 2 N NaOH. Acidification of the basic water solution gave 1.55 g of an acid (~ 8 %), a sample of which was dissolved in ether and silylated with BSA. Combined vpc-ms analysis (column SE 30, 3 %, 150-200°C, 4°/min) showed the presence of two components with the relative percentages 25:75, and m/e 228 and 344, respectively. The most abundant component was the least volatile one. By mixing the above sample with authentic silylated 2,5-dimethyl-3-thiophenecarboxylic acid, it was shown after vpc analysis (column as above), that the most volatile component was the trimethylsilyl ester of this acid. The most abundant component had a shorter retention time than that of the authentic silylated 3-carboxyl-2-methyl-5-thienylacetic acid (100), as shown by a "mixing" analysis (as above). (Retention times 9.5 and 10.6 minutes for silylated 97 and 100, respectively.)

The pure title acid (97), m.p. 217-219°C, was obtained through recrystallization from a mixture of methanol, chloroform and hexane (2:20:10). Ir: C=O 1700 cm⁻¹ and 1640 cm⁻¹. Nmr (DMSO-d₆): $\delta_{4H} = 7.04$ ppm (q, 1H); $\delta_{5CH_3} = 2.38$ ppm (d, 3H); $\delta_{2-CH_2-} = 4.06$ ppm (s, 2H). $J_{4H, 5CH_3} = 1.1$ Hz. [Found: C 47.8; H 4.18; S 15.9. Calc. for C₈H₈O₄S (200.21): C 48.00; H 4.03; S 16.01.]

b) To 143 ml (0.20 mol) of 1.4 M butyllithium in hexane, 23.2 g (0.200 mol) of TMEDA was added. After ten minutes, 11.2 g (0.100 mol) of 2,5-dimethylthiophene was added rapidly. A yellow precipitate was formed and the reaction mixture was allowed to stand at room temperature (~ 21°C) for 2 h, whereupon it was poured onto solid carbon dioxide in ether. The carbonated mixture was extracted with 1 N NaOH (3x100 ml) and the collected

water portions were extracted with ether. After acidification of the water phase it was again extracted with ether (3x50 ml). A sample of this ether phase was silylated with BSA and analyzed by vpc (column SE30, 3%, 150-200°C, 4°/min). Three components were found in the proportions (retention times in minutes) 2(2.6): 8(2.9):90(9.5). The latter two were identical with those in experiment a). The first one was not identified. No traces of compounds with longer retention times were found.

After evaporation of the ether, 3.2 g of the crude acid mixture was collected; yield 16 % (17 % was reported in Ref. 96, but no details were given).

Ring-opening experiment on 2,5-dimethylthiophene with ethyllithium:TMEDA. To 130 ml (0.100 mol) of 0.77 M ethereal ethyllithium, 11.6 g (0.100 mol) of TMEDA was added. To this mixture, 11.2 g (0.100 mol) of 2,5-dimethylthiophene was added in a rapid stream. The reaction mixture was refluxed for 2 h (a yellow precipitate was formed), whereupon 42.6 g (0.300 mol) of methyl iodide was added. Reflux was maintained for another hour, after which the mixture was hydrolyzed with water. The ether phase was washed with 2 N HCl and water to neutral reaction. Vpc (column OV 17, 3 %, 80-190°C, 4°/min) of the dried ether phase showed 10 components, of which the starting material amounted to about 80 %. Evaporation left 3.0 g of crude product not containing 2,5-dimethylthiophene. Ir: $\equiv\text{CH}$ 3280 cm^{-1} , C=C 2210 and 2080 cm^{-1} . Nmr (CCl_4) of the crude product: δ = 3.1 ppm ($\equiv\text{CH}$ and/or $-\text{CH}_2-\text{C}\equiv\text{C}$); δ = 5.25-5.70 ppm (m, C=CH-) and several lines in the methyl region. There were no absorptions in the aromatic region. A combined vpc-ms analysis (column BDS, 10 %, 125°C) of the crude mixture gave the following data:

peak no	1	2	3	4	5	6	7	8	9
rel. %	22	27	18	10	7	2	5	2	6
retention time									
(min.)	7.4	8.2	9.0	9.5	11.5	12	13	14	15
m/e	140	154	154	154	168		168		168

Peaks nos. 6 and 8 were too small to give reliable mass numbers. For possible structures, see p 44. No attempts were made to isolate any of the compounds.

3,4,5-Trimethyl-2-thienylacetic acid (102). A solution of 5.8 g (0.050 mol) of TMEDA in 25 ml of ether was added to 63 ml (0.050 mol) of 0.80 M ethyllithium in ether. After 10 minutes, 7.0 g (0.050 mol) of tetramethylthiophene (101) in 50 ml of ether was added all at once. Additional ether was supplied to a total volume of 150 ml, and the mixture was refluxed for 2 h (ether was added to maintain 150 ml). At this point, 50 ml of the mixture was withdrawn with a pipette and poured onto solid carbon dioxide in ether. To the remainder, 11 g (0.10 mol) of ethyl bromide was added and reflux was continued for another hour. The ether phase was washed with water, dil. HCl and water to neutral reaction and dried. Evaporation left 4.1 g of an oil. Ir: $\equiv\text{CH}$ 3300 cm^{-1} , $\text{C}\equiv\text{C}$ 2100, 2080 cm^{-1} . Vpc-ms (OV17, 3%, 100-250°C, 12°/min) showed 15 components, of which the most abundant was the starting material (~60 %). A component with $m/e = 168$ amounted to ~20 % and could have the structure suggested in 2.6, where the mass spectrum is discussed. Nmr (CCl_4) showed mainly the starting material; $\delta = 2.20$ ppm and $\delta = 1.90$ ppm. Other signals were present in the aliphatic region, but could not be assigned to any specific structure. Attempted distillation of the crude product at reduced pressure was unsuccessful due to tar formation, and preparative tlc (silica gel, hexane: ether 9:1) gave no significant separation.

The carbonated ethereal portion was extracted with dil. NaOH solution and the collected basic water portions were acidified, giving 0.15 g of the title compound; yield 5 %, m.p. ~ 110°C. Recrystallization from hexane gave the pure acid, m.p. 116-118°C. Ir: $\text{C}=\text{O}$ 1710 cm^{-1} . Nmr (CDCl_3): $\delta_{2-\text{CH}_2} = 3.67$ ppm (s, 2H); $\delta_{\text{CH}_3} = 2.30$ ppm (s, 3H); $\delta_{\text{CH}_3} = 2.00$ ppm (m, 6H); $\delta_{\text{COOH}} = 11.0$ ppm (s, 1H). [Found: C 58.6; H 6.42; S 17.4. Calc. for $\text{C}_9\text{H}_{12}\text{O}_2\text{S}$ (184.26): C 58.67; H 6.56; S 17.40.]

Experimental part of chapter 2.7

Ring-opening attempt on 3-bromo-5-methyl-2-thiophenecarboxylic acid (125). The general method G was followed. From 2.21 g (0.0100 mol) of 3-bromo-5-methyl-2-thiophenecarboxylic acid (125) in 50 ml of ether, 63 ml (0.025 mol) of 0.40 M

ethereal ethyllithium and 5.45 g (0.0500 mol) of ethyl bromide, 1.15 g of a neutral crude product was obtained. Upon acidification of the basic extracts, no carboxylic acid could be isolated. The crude product contained 6 components according to vpc analysis (column OV 17, 3 %, 70-295°C, 10°/min). Ir: OH 3450 and 3300 cm⁻¹, C=O 1660 cm⁻¹. No acetylenic absorptions around 2100 cm⁻¹ were present. Attempts to isolate any of the components were not made.

The addition of ethylthiolate to 6,6-dimethyl-2,4-heptadiyne (108). A mixture of 1.10 g (9.17 mmol) of 108, 1.13 g (18.2 mmol) of ethanethiol and 0.11 g of KOH in 4 ml of methanol was heated to 120°C for 3.5 h in a 10 ml Pyrex ampoule. The reaction mixture was poured into water, which was extracted several times with ether. Vpc analysis (column OV 1, 3 %, 110-260°C, 10°/min) of the dried ethereal solution showed mainly one component (~ 70 %) with the same retention time as (Z)-2-ethylthio-6,6-dimethyl-2-hepten-4-yne (26) together with 30 % of 108. Evaporation of the solvent and the remaining starting material yielded 1.1 g (65 %) of crude 26. Nmr (CCl₄) of the crude product was identical with that of 26 but different from that of 30. The same was true for an ir spectrum.

The addition of ethylthiolate to 2,4-heptadiyne (109). With the same method as in the preceding experiment, a mixture of (Z)-2-ethylthio-2-hepten-4-yne (17) and (Z)-3-ethylthio-3-hepten-5-yne (22) in the proportions 60:40 (vpc, column OV 17, 3 %, 80-200°C, 10°/min) was obtained from 3.69 g (40.1 mmol) of 109, 5.0 g (81 mmol) of ethanethiol and 0.3 g of KOH in 6 ml of methanol. The identification of the components was performed by comparison of the retention times with those of authentic samples of 17 and 22 ("mixing" analysis). Evaporation of the solvent and the remaining starting material gave 3.7 g (52 %) of crude product.

6,6-Dimethyl-2,4-heptadiyne (108). To 12.2 g (0.0300 mol) of 2-t-butyl-3,4-diiodo-5-methylthiophene (106) in 100 ml of ether, 100 ml (0.065 mol) of 0.65 M ethereal ethyllithium was added at -70°C followed by 4.7 g (0.030 mol) of ethyl iodide. After 1 h, the reaction mixture was allowed to reach room temperature and kept there for 4 h, whereupon it was poured onto

solid carbon dioxide in ether. No carboxylic acid could be isolated from the basic extracts upon acidification. The neutral ethereal phase was dried and the solvent was removed by distillation at ordinary pressure. The title compound was obtained at reduced pressure, b.p.₁₄ 57-59°C, 2.1 g (58 %). n_D^{22} 1.4780 (lit.^{44a} b.p.₁₀ 51-51.5°C, n_D^{20} 1.4802). Ir: C≡C 2195, 2155 and 2040 cm^{-1} (lit.^{44a} 2192, 2151 and 2030 cm^{-1}).

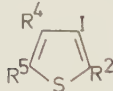
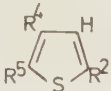
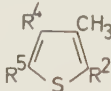
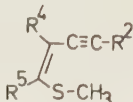
2,4-Hexadiyne (107). With the same procedure as in the preceding experiment, compound 107 was obtained from 36.4 g (0.100 mol) of 3,4-diiodo-2,5-dimethylthiophene⁵² (105) in 1 l of ether, 250 ml (0.20 mol) of 0.80 M ethereal ethyllithium and 15.6 g (0.100 mol) of ethyl iodide. The dried neutral ethereal extract was concentrated to half its volume and the residue was cooled to -70°C, whereupon the crystals were collected by suction. Repeated concentration of the filtrates and cooling gave a total of 5.0 g (54 %) of the title compound, m.p. 67-68°C (lit.^{84d} 66-67°C).

Experimental part of chapter 2.8

Preliminary experiments for the kinetic measurements. The compounds 8, 59, 52 and 61 were all treated in the same way. To 5.00 mmol of each compound in 10 ml of ether, 5.50 ml of 1.0 M ethereal phenyllithium was added (with a syringe), after which samples were withdrawn and quenched with an excess of DMS in ether at different times. All operations were performed in a glove-box supplied with dry (2 rel %) oxygen-free nitrogen. The samples were subsequently analyzed by vpc (column OV 17, 3 %, 100-250°C, 10°/min), and the results are presented below. In all cases the starting material was consumed (<0.1 rel%) within 30 sec. This was also the case when 8 and phenyllithium were reacted at -30°C in an analogous experiment. The dehalogenated heterocycles and the enyne thioethers were identified upon comparison of the retention times with those of authentic samples. Combined vpc-ms analysis of samples from the reaction mixtures gave mass numbers in agreement with the proposed structures. (Table 4.)

The effect of a heterogeneous system. To a solution of 2.38 g (0.0100 mol) of 2,5-dimethyl-3-iodothiophene (8) in 3.5 ml of hexane, 7.1 ml (0.010 mol) of 1.42 M butyllithium in

Table 4. The reaction between some iodothiophenes and phenyllithium in ether at 21°C. The reaction was followed by quenching samples from the reaction mixtures with DMS.

Starting material	time (min)	products (rel %)		
				
$R^2=R^5=CH_3, R^4=H$	0.5	1	81	19
	1.0		64	36
	2.0		27	73
	3.0		15	85
	5.0		4	96
	10.0		0	100
$R^2=CH_3, R^5=C_6H_5, R^4=H^*$	0.5	7	93	0
	5.0	6	63	30
	20.0	4	24	71
	30.0	4	13	83
	60.0	6	2	92
	80.0	8	0	92
$R^2=C_6H_5, R^5=CH_3, R^4=H$	0.5	12	83	5
	1.0	10	80	10
	5.0	9	60	31
	10.0	12	46	42
	20.0	10	31	59
	30.0	13	15	72
	40.0	11	12	77
	120.0	10	0	90
$R^2=R^5=CH_3, R^4=C_6H_5$	0.5	8	92	0
	5.0	10	86	4
	20.0	11	67	22
	60.0	10	27	63
	80.0	7	14	78
	120.0	6	2	92

* Several unidentified compounds with longer retention time, amounting to ~ 15 %, were also present.

hexane was added at room temperature. A light yellow precipitate was formed. The reaction was followed by quenching samples of the reaction mixture with dimethyl sulphate. The experiment was performed in a glove-box supplied with dry (2 rel %) oxygen-free nitrogen. Vpc analysis (column BDS, 10 %, 90-190°C, 10°/min) of the samples gave the following results.

time (min)	2,3,5-trimethylthiophene rel %	comp. <u>11a</u>
0.5	100	0
10.0	91	9
20.0	18	82
240	0	100

Kinetic measurements

Determination of the apparent reaction order for the formation of E, F, G, H, and I (see Table 1). Samples of the compounds 8 (0.105 g, 0.441 mmol), 29 (0.112 g, 0.400 mmol), 110 (0.113 g, 0.403 mmol), 61 (0.075 g, 0.25 mmol) and 59 (0.120 g, 0.400 mmol) were placed in nmr tubes which were sealed with plastic caps and cooled to -70°C in ethanol/solid carbon dioxide. An excess of 1.0 M phenyllithium (0.50 ml, and in the case of 61 0.30 ml), prepared from iodobenzene and lithium in ether, was then injected with a syringe. No precautions to exclude air from the nmr tubes were taken. The tubes were sealed off and stored at -70°C until just before the measurement, when they were heated to -30°C (in the case of 8 and 110) and to +20°C (in the case of 59, 61, and 29) and turned upside-down a couple of times in order to mix the reagents, whereupon they were placed in the probe of the nmr spectrometer at a pre-set temperature. The increasing vinylic absorptions of the enyne-thiolates (E-I) were then integrated at different times. The final integral values, $I_{g_{tot}}$, were obtained by heating the tubes to +35°C for 30 min after the measurements. It was assumed that the reactions were thus completed. (Cf. the preliminary experiments.) The primary data are presented below (t = time, I_g = integral).

Substance E

t(min)	0	0.5	1.0	2.0	2.5	3.0	3.5	4.0	4.5	5.0	
Ig(mm)	24	31	35	44	50	56	59	65	68	73	
t(min)	5.5	6.5	7.0	7.5	8.0	9.0	9.5	10.5	11.0	11.5	12.0
Ig(mm)	78	84	87	89	93	96	99	102	108	110	113
t(min)	12.5	14.0	15.0	15.5	16.0	16.5	17.0	17.5	18.0	18.5	
Ig(mm)	117	122	123	124	127	128	132	133	132	134	
t(min)	19.0	19.5									
Ig(mm)	135	137									
											Ig _{tot} = 153

Substance F

t (min)	0	2	5	7	9	11	13	15	17	
Ig (mm)	53	60	71	77	81	91	96	100	105	
t (min)	19	21	23	25	27	29	31	33		
Ig (mm)	113	122	128	133	138	142	146	156		
t (min)	37	39	64	66	69	72				
Ig (mm)	162	160	184	187	189	190				Ig _{tot} = 201

Substance G

t (min)	0	2	4	6	8	13	17	19	30	
Ig (mm)	25	26	25	25	24	30	31	31	40	
t (min)	32	42	44	47	63	66	68	87		
Ig (mm)	40	44	45	48	52	55	55	62		
t (min)	89	92	112	122						
Ig (mm)	62	62	67	68						Ig _{tot} = 79

Substance H

t (min)	0	2	7	12	17	22	27	32	42	
Ig (mm)	36	40	45	47	49	45	51	50	52	
t (min)	57	72	82	87	107	123	142	153		
Ig (mm)	56	60	65	64	75	76	85	87		
t (min)	182	187	198	213	227	242	257			
Ig (mm)	92	94	97	103	106	111	111			Ig _{tot} = 167

Substance I

t(min)	0	13	36	78	103	133	149			
Ig(mm)	6	8	15	19	24	31	35			

t(min)	198	223	253	283	313
Ig(mm)	41	47	52	53	61

$$I_{g_{tot}} = 174$$

Least-squares fitting of the data to the expression $\ln \frac{I_{g_{tot}}}{I_{g_{tot}} - I_g} = k \times t + 1$ (first-order rate expression with respect to the enyne thiolates) gave the rate constants presented in Table 1.

Activation parameters for the formation of E. Five samples (0.096-0.104 g, 0.403-0.437 mmol) of compound 8 were placed in nmr tubes and treated with phenyllithium (the same batch) as described above. The rate of formation of E was measured as above at five different temperatures, and the data are presented below (T = temperature ($^{\circ}\text{C}$), t = time (min), Ig = integral value (mm)). T = -0.5°C (the data are presented in the preceding experiment).

$$T = -8.5^{\circ}\text{C}$$

t(min)	0	1	2	3	4	5	6	7	8	9	10	11
Ig(mm)	43	48	54	60	65	70	76	82	86	91	95	100
t(min)	12	13	15	17	18	19	21	23	26.5			
Ig(mm)	108	109	111	119	121	126	134	138	146			
t(min)	28.5	32.5	34.5									
Ig(mm)	150	155	157									

$$I_{g_{tot}} = 176$$

$$T = -17.0^{\circ}\text{C}$$

t(min)	0	2	4	6	8	11.5	13	15	18	20	22
Ig(mm)	27	31	37	45	48	52	55	62	63	68	72
t(min)	25	27	30	33	35	38	40	43	46	50	
Ig(mm)	78	85	91	92	94	102	103	108	114	116	
t(min)	53	57	60	71	76	82					
Ig(mm)	123	125	129	136	140	147					

$$I_{g_{tot}} = 188$$

$$T = -18.0^{\circ}\text{C}$$

t(min)	0	3	6	9	15	18	21	24	27	30
Ig(mm)	49	54	58	71	75	79	84	89	91	94
t(min)	33	36	42	47	50	55	58			
Ig(mm)	100	105	107	115	115	116	123			
t(min)	64	67	70	73	76	79	82			
Ig(mm)	129	126	127	130	131	135	138			

$$I_{g_{tot}} = 178$$

$$T = -21.0^{\circ}\text{C}$$

t(min)	0	5	9	14	19	29	44	54	64	74
Ig(mm)	16	21	22	22	25	31	35	40	42	45
t(min)	84	94	109	124	144	159	174	205		
Ig(mm)	47	51	56	58	65	65	66	72		
t(min)	229	244	274							
Ig(mm)	73	75	78							

$$I_{g_{\text{tot}}} = 95$$

$$T = -29.0^{\circ}\text{C}$$

t(min)	0	6	10	29	49	53	58	63	68	73
Ig(mm)	33	38	36	47	47	51	53	54	53	57
t(min)	83	93	113	123	143	184	189	195		
Ig(mm)	53	56	59	65	69	75	74	76		
t(min)	202	242	257	294	342					
Ig(mm)	81	91	94	98	103					

$$I_{g_{\text{tot}}} = 132$$

The rate constants were obtained as mentioned above and are presented in Table 2. The Eyring equation gave the activation parameters when $\ln \frac{k}{T}$ was plotted against $\frac{1}{T}$ (T $^{\circ}\text{K}$) (Table 2).

Error estimation. Each integral value was taken as the mean of three integrations, except for E at -0.5°C , in which case only one integration was made at each time. The error in Ig (mean integral value) is estimated to be ± 2 mm, giving an error in the rate constants of ± 10 %, when varying the first and last integral values in each case but keeping the time parameter constant. By varying also this in the extreme points the error in the rate constants would increase only slightly, since the estimated time control was ± 2 seconds. The estimated temperature variation was $\pm 0.25^{\circ}\text{C}$, giving an error in the individual rate constants of ± 3 % (cf. Ref. 176 for formula). This crude error estimation suggests that the rate constants are determined within about ± 15 %, which would allow $\Delta H^{\ddagger}$ to be determined with an accuracy of ± 8 % (cf. the standard deviation was ± 6 %, Table 2). Since systematic errors have not been considered the $\Delta S^{\ddagger}$ value determined must be regarded as very uncertain.

Experimental part of Chapter 3.1

2,5-Dimethylfuran.¹⁷⁷ This compound was prepared according to Ref. 116 in 68 % yield from 228 g (2.00 mol) of acetonyl-acetone, 224 g (2.20 mol) of acetic anhydride and 2 g of zinc chloride (dry), b.p. 92-94°C (130 g; lit.¹¹⁶ b.p. 92.5-94°C, 71 %).

3-Iodo-2,5-dimethylfuran¹¹⁷ (34) was prepared according to Ref. 117. A mixture of 50 g (0.52 mol) of 2,5-dimethylfuran, 140 g (0.52 mol) of mercury(II) dioxide and 65 g of sodium acetate in 750 ml of water gave 120 g of crude 2,5-dimethyl-3-furylmercury chloride, 90 g of which was treated with an aqueous iodine-potassium iodide solution until the iodine colour persisted. After work-up and distillation, 32.3 g (28 %) of the title compound was obtained based on 2,5-dimethylfuran; b.p.¹² 67-68°C. (Lit.¹¹⁷ b.p.₂₀ 85-86°C.) There remained 15.5 g of 3,4-diiodo-2,5-dimethylfuran¹¹⁷ in the distillation flask.

Experimental part of Chapter 3.2

Selenophene (46).

a) According to the procedure of Briscoe et al.,^{123,124} a sample of 15 g (0.19 mol) powdered grey elemental selenium in a porcelain crucible was introduced into a Pyrex tube placed in a tube oven. Acetylene, which was led through wash bottles with water and sulphuric acid (in that order), was bubbled through the tube at a rate of about 8 bubbles/second. The oven temperature was slowly increased to 400°C. After some minutes there was a flash in the tube and a black deposit was formed which started the production of a brown pyrolysate. The reaction subsided after 5-6 h, and about 5 g of pyrolysate was collected. Combined vpc-ms analysis (column BDS, 10 %, 70-170°C, 6°/min) showed that benzene, toluene and selenophene were present in the proportions 70:10:20, together with several high boiling components.^{80b,186} Distillation gave three fractions 1) b.p. 80-106°C, 2.0 g consisting of almost pure benzene, 2) b.p. 106-113°C, 0.5 g consisting of a mixture of benzene, toluene and selenophene and 3) b.p. 113-121°C, 1.2 g, containing toluene and

selenophene (20:80). An experiment with commercial acetone-free acetylene gave essentially the same result.

b) A Pyrex tube was supplied with 10 g of selenium in portions, with alumina (1 mm pellets) between the portions of selenium (cf. Ref. 129) until the tube was filled, whereupon it was placed in a tube oven and acetylene (without purification) was bubbled through as mentioned above. After 2 h at 340-360°C, the reaction subsided and 7.5 g of pyrolysate was collected, which gave 5.4 g (33 %) of selenophene, b.p. 110-115°C, upon distillation. This selenophene contained ~ 2 % of toluene (vpc as above). For large-scale synthesis of selenophene, a tube oven with 10 tubes was constructed as shown in Fig. 2. Each tube was supplied with 20 g of selenium and alumina, which gave about 100 g of selenophene per run under optimal conditions (6-8 bubbles/second and an oven temperature of 340°C). Tube dimensions: length 660 mm, i.d. 25 mm.

Experimental part of Chapter 3.3.1

2,5-Dimethylselenophene¹³⁴ (111). A mixture of 114 g (1.00 mol) of acetonylacetone and 110 g (0.241 mol) of powdered phosphorous pentaselenide (P_2Se_5) was heated in a closed stainless steel cylinder at 180°C for 4 h. After cooling, the tube was opened in a hood and the contents poured into 2 N NaOH and steam distilled. The organic layer was separated, dried and distilled. Thus 30.8 g (19 %) of the title compound was obtained, b.p. 153-160°C (lit.¹³⁴ b.p. 153-155°C). P_2Se_5 was prepared by fusing stoichiometric amounts of red phosphorous and grey selenium under nitrogen.¹⁷⁸

2,5-Dimethyl-3-iodoselenophene¹ (1). To a mixture of 220 ml of water, 170 ml of acetic acid, 1.1 ml of conc. sulphuric acid, 110 ml of carbon tetrachloride, and 90.0 g (0.566 mol) of 2,5-dimethylselenophene, 25.5 g (0.145 mol) of iodic acid in 100 ml of water and 73.6 g (0.290 mol) of iodine were added in portions with vigorous stirring at 40°C. The addition took 1.5 h, whereupon the mixture was stirred at 40°C for 2.5 h and then poured into 150 ml of a saturated sodium thiosulphate solution. The organic layer was separated and the aqueous phase extracted

with carbon tetrachloride. The combined organic phases were washed with water, dried and fractionated to yield 119.4 g (74 %) of 1, b.p.₃ 87-90°C, $n_D^{20} = 1.6483$. Nmr (CCl_4): $\delta_{2\text{CH}_3} = 2.39$ ppm (bs, 3H); $\delta_{5\text{CH}_3} = 2.50$ ppm (m, 3H); $\delta_{4\text{H}} = 6.70$ ppm (q, 1H); $J_{5\text{CH}_3, 4\text{H}} = 1.2$ Hz. [Found: C 25.15; H 2.68; m/e = 286. Calc. for $\text{C}_6\text{H}_7\text{ISe}$ (284.99): C 25.29; H 2.48.]

2,5-Dimethyl-3-iodothiophene⁵² (8) was prepared according to Ref. 52 and was available at this institute.

2,3,5-Trimethylthiophene¹³⁶ (113). A solution of 50.0 g (0.210 mol) of 2,5-dimethyl-3-iodothiophene (8) in 100 ml of ether was cooled to -70°C, and 146 ml (0.22 mol) of 1.5 M butyllithium in hexane was added, followed by 27.7 g (0.220 mol) of dimethyl sulphate in 100 ml of ether (very slowly). The mixture was stirred at -70°C for 1.5 h, whereupon the cooling bath was removed and the reaction mixture was allowed to reach room temperature. Conc. ammonium hydroxide was added and the ethereal layer was separated, washed with 2 N HCl, water and dried. Evaporation and distillation gave 14.9 g (56 %) of the title compound, b.p. 161-163°C (lit.¹³⁶ b.p. 163°C).

4-Iodo-2,3,5-trimethylthiophene (32). A mixture of 12.6 g (0.100 mol) of 2,3,5-trimethylthiophene (113), 35 ml of acetic acid, 40 ml of water, 35 ml of CCl_4 , 4.40 g (0.025 mol) of iodic acid and 4 drops of conc. H_2SO_4 was warmed to 40°C, whereupon 12.7 g (0.0500 mol) of iodine was added in portions (vigorous stirring). When the addition was complete, the temperature was raised to 60°C. After 2 h the reaction mixture was poured into aqueous sodium thiosulphate and extracted with CCl_4 . The organic portions were washed with water, dried, evaporated and distilled, giving 15.0 g (59 %) of the title compound, b.p._{0.7} 67-68°C. Nmr (CCl_4): $\delta_{\text{CH}_3} = 2.07$ ppm (s, 3H) and 2.30 ppm (bs, 6H). [Found: C 33.41; H 3.63; ^3S 12.75. Calc. for $\text{C}_7\text{H}_9\text{IS}$ (252.12): C 33.35; H 3.60; S 12.72.]

3,4-Diiodo-2,5-dimethylthiophene¹⁷⁹ (105) was prepared according to Ref. 52 from 32.0 g (0.286 mol) of 2,5-dimethylthiophene, 58.4 g (0.230 mol) of iodine, 23.0 g (0.131 mol) of iodic acid, 80 ml of acetic acid, 30 ml of water, 20 ml of CCl_4 and 3 ml of conc. H_2SO_4 in a 61 % yield (63 g) after recrystalli-

zation from petroleum ether (65-70°C), m.p. 81-83°C (lit.¹⁷⁹ 83°C).

3-(1-Cyclohexenyl)-2,5-dimethylthiophene¹³⁷ (114). The procedure in Ref. 137 was followed. To 47.6 g (0.200 mol) of 3-iodo-2,5-dimethylthiophene in 100 ml of ether, 158 ml (0.205 mol) of 1.30 M ethereal butyllithium was added at -70°C, followed by 20.1 g (0.205 mol) of cyclohexanone in 100 ml of ether. After work-up and distillation, 21.0 g (55 %) of the title compound was obtained, b.p._{0.3} 88-90°C (lit.¹³⁷ b.p.₈ 134-136°C).

2,5-Dimethyl-3-phenylthiophene¹³⁸ (53). A mixture of 19.2 g (0.100 mol) of 3-(1-cyclohexenyl)-2,5-dimethylthiophene (114) and 49 g (0.20 mol) of chloranil was refluxed in 260 ml of chlorobenzene for 4 h. After cooling, the reaction mixture was filtered and the chlorobenzene was evaporated. The residue was dissolved in ether and washed with 5 N aq. NaOH several times and with water to neutral reaction, and dried. Evaporation of the solvent and distillation gave 10.0 g (53 %) of the title compound, b.p._{0.8} 98-100°C. $n_D^{20} = 1.6031$ (lit.¹³⁷ b.p.₁₀ 140-143°C, $n_D^{20} = 1.6052$).

3-Iodo-2,5-dimethyl-4-phenylthiophene (52). A mixture of 5.00 g (26.6 mmol) of 2,5-dimethyl-3-phenylthiophene (53), 3.6 g (14 mmol) of iodine, 1.2 g (6.8 mmol) of iodic acid, 15 ml of acetic acid, 20 ml of water, 15 ml of CCl₄ and 0.1 ml of conc. H₂SO₄ was stirred vigorously at 60°C for 4.5 h. After cooling, the reaction mixture was poured into aqueous sodium thiosulphate and extracted with CCl₄. The organic portions were washed with water, dried and the solvent was evaporated. The crystalline residue, 7.5 g (90 %), was recrystallized from hexane in the cold (-25°C) giving 6.5 g (79 %) of the pure title compound, m.p. 53-56°C. Nmr (CCl₄): $\delta_{C_6H_5} = 7.1-7.5$ ppm (m, 5H); $\delta_{CH_3} = 2.40$ ppm (s, 3H) and 2.27 ppm (s, 3H). [Found: C 45.90; H 3.60; S 10.16. Calc. for C₁₂H₁₁IS (314.19): C 45.87; H 3.53; S 10.21.]

Tetramethylthiophene¹⁷⁴ (101). From 30.0 g (0.268 mol) of 2,5-dimethylthiophene, 72.4 g (0.804 mol) of sym. trioxane and HCl gas, 40.2 g (72 %) of crude 3,4-bis(chloromethyl)-2,5-dimethylthiophene (117) was obtained, m.p. 68-69°C (lit.¹¹⁶ m.p. 73°C). The bis(chloromethyl) compound, 40.0 g (0.191 mol), was subsequently reduced with 16.8 g (0.443 mol) of lithium aluminum

hydride in ether to give the title compound; yield 17.3 g (65 %), b.p.₁₂ 76-77°C (lit.¹¹⁶ b.p.₁₂ 74-79°C, 67 %).

3-Acetyl-2,4,5-trimethylthiophene (118). To a mixture of 1.00 g (7.92 mmol) of 2,3,5-trimethylthiophene (113) and 1.30 g (12.7 mmol) of acetic anhydride, 1 drop of 70 % perchloric acid was added. Heat was evolved and the reaction mixture was stirred at room temperature overnight. It was then poured into water, extracted with ether and the ether phases washed with water to neutral reaction. After drying and evaporation of the solvent, 1.1 g of crude product remained, which was distilled, b.p._{0.5} 74-75°C, 0.75 g (56 %). Nmr (CCl₄): $\delta_{\text{CH}_3 \text{ aromatic}} = 2.45 \text{ ppm}$, 2.22 ppm and 2.10 ppm, all broadened singlets with fine structure; $\delta_{\text{COCH}_3} = 2.32 \text{ ppm (s)}$. [Found: C 64.0; H 7.19; S 19.0. Calc. for C₉H₁₂OS (168.26): C 64.25; H 7.19; S 19.06.]

2,4,5-Trimethyl-3-thienylacetic acid (103). A mixture of 0.50 g (3.0 mmol) of 3-acetyl-2,4,5-trimethylthiophene (118), 1.6 g (3.6 mmol) of thallium trinitrate trihydrate and 1.0 ml of 70 % perchloric acid in 5 ml of methanol was stirred at room temperature for 18 h. The precipitated thallium mononitrate was filtered off, and 50 ml of water was added to the filtrate. After extraction with CHCl₃, drying and evaporation of the solvent, 0.55 g of a brown oil remained. This oil (the methyl ester of the title compound according to nmr) was refluxed in a mixture of 2 g of potassium hydroxide, 10 ml of water and 10 ml of ethanol for 4 h. The ethanol was evaporated and the residual solution acidified with dilute HCl. Thus, 0.35 g (63 %) of the title compound was isolated, m.p. 100-102°C. Recrystallization from hexane in the cold (-25°C) gave the pure acid, m.p. 104-106°C. Nmr (DMSO-d₆): $\delta_{\text{CH}_3} = 1.95 \text{ ppm (s, 3H)}$ and 2.23 ppm (bs, 6H); $\delta_{3\text{-CH}_2\text{-}} = 3.37 \text{ ppm (s, 2H)}$. Ir: C=O 1705 cm⁻¹. [Found: C 58.4; H 6.63; S 17.1. Calc. for C₉H₁₂O₂S (184.26): C 58.67; H 6.56; S 17.40.]

Experimental part of Chapter 3.3.2

4-Bromo-2-methylthiophene¹⁴¹ (121) was prepared according to Ref. 180 from 121 g (0.500 mol) of 2,4-dibromothiophene, 321 ml (0.510 mol) of 1.59 M butyllithium in hexane and 69 g

(0.55 mol) of DMS in a 96 % yield (85 g), b.p.₁₀ 63-70°C (lit.¹⁴¹ b.p.₁₁ 61-62°C).

4-Bromo-2-methylselenophene (122) was prepared as above in 95 % (crude) yield (26.3 g) from 35.5 g (0.123 mol) of 2,4-dibromoselenophene (120) in 150 ml of ether, 96.0 ml (0.125 mol) of 1.30 M butyllithium in hexane and 44 g (0.35 mol) of DMS. Part of the crude product was distilled, giving pure 122, b.p.₁₅ 83-85°C. Nmr (CCl₄): $\delta_{2\text{CH}_3} = 2.50$ ppm (d, 3H); $\delta_{3\text{H}} = 6.75$ ppm (pentet, 1H); $\delta_{5\text{H}} = 7.45$ ppm (d, 1H). $J_{3\text{H}, 5\text{H}} = 1.4$ Hz; $J_{2\text{CH}_3, 3\text{H}} = 1.2$ Hz. [Found: C 26.80; H 2.20; Se 35.22. Calc. for C₅H₅BrSe (223.96): C 26.82; H 2.25; Se 35.27.]

2,3-Dibromo-5-methylthiophene⁶¹ (123) was prepared according to Ref. 61 from 30.7 g (0.173 mol) of 4-bromo-2-methylthiophene (121), 27.8 g (0.174 mol) of bromine in 500 ml of acetic acid in 72 % yield (32.0 g), b.p._{1.0} 60-65°C (lit.⁶¹ b.p.₁₁ 107-115°C).

2,3-Dibromo-5-methylselenophene (124). To a solution of 18.8 g (0.0839 mol) of crude 4-bromo-2-methylselenophene (122) in 200 ml of carbon disulphide, 13.5 g (0.084 mol) of bromine in 50 ml of acetic acid was added dropwise at -30°C. When the addition was complete, nitrogen gas was led through the reaction mixture while it was allowed to reach room temperature. In this way some of the hydrogen bromide, formed in the reaction, was quickly removed. The mixture was poured into aq. sodium thiosulphate and extracted with carbon disulphide. The organic portions were washed with water and dried. After evaporation of the solvent, 15.9 g (63 %) of homogeneous crude product remained (vpc: column BDS, 10 %, 100-195°C, 12°/min), part of which was distilled giving the pure title compound, b.p._{1.0} 75-76°C. Nmr (CCl₄): $\delta_{5\text{CH}_3} = 2.43$ ppm (d, 3H); $\delta_{4\text{H}} = 6.64$ ppm (q, 1H) $J_{5\text{CH}_3, 4\text{H}} = 1.2$ Hz. [Found: C 19.76; H 1.24; Br 52.89; Se 26.00. Calc. for C₅H₄Br₂Se (302.86): C 19.83; H 1.33; Br 52.77; Se 26.07.]

3-Bromo-5-methyl-2-methylthiothiophene^{82a} (80). The procedure described in Ref. 145 was followed. From 28.3 g (0.110 mol) of 2,3-dibromo-5-methylthiophene (123) in 100 ml of ether, 70 ml (0.11 mol) of 1.60 M butyllithium in hexane and

10.5 g (0.112 mol) of dimethyl disulphide in 100 ml of ether, 16.2 g (66 %) of the title compound was isolated after distillation, b.p._{1.0} 75-80°C (lit.^{82a} b.p.₂ 86-87°C). Nmr (CCl₄): δ_{SCH_3} = 2.33 ppm (s); δ_{SCH_3} = 2.38 ppm (d); $\delta_{4\text{H}}$ = 6.59 ppm (q). $J_{\text{SCH}_3, 4\text{H}}$ = 1.1 Hz.

3-Bromo-5-methyl-2-methylthioselenophene (85) was prepared as above in 56 % yield (5.28 g) from 10.6 g (0.0350 mol) of 2,3-dibromo-5-methylselenophene (124) in 100 ml of ether, 21 ml (0.036 mol) of 1.70 M butyllithium in hexane and 3.8 g (0.040 mol) of dimethyl disulphide, b.p.₃ 100-110°C. Nmr (CCl₄): δ_{SCH_3} = 2.40 ppm (s, 3H); δ_{SCH_3} = 2.49 ppm (d, 3H); $\delta_{4\text{H}}$ = 6.72 ppm (q, 1H). $J_{\text{SCH}_3, 4\text{H}}$ = 1.4 Hz. [Found: C 26.71; H 2.56; Br 29.68; S 11.81; Se 29.22. Calc. for C₆H₇BrSSe (270.05): C 26.69; H 2.61; Br 29.59; S 11.87; Se 29.24.]

5-Methyl-2,3-dimethylthiophene (83). From 2.23 g (0.0100 mol) of 3-bromo-5-methyl-2-methylthiophene (80) in 50 ml of ether, 7.0 ml (0.011 mol) of 1.60 M butyllithium in hexane and 1.13 g (0.012 mol) of dimethyl disulphide in 25 ml of ether, 1.60 g of crude title compound was obtained according to the preceding procedure (Ref. 145). Distillation gave 0.72 g (38 %) of pure 83, b.p._{1.0} 94-96°C. Nmr (CCl₄): δ_{SCH_3} = 2.38 ppm (d); $\delta_{4\text{H}}$ = 6.51 ppm (q); δ_{SCH_3} = 2.32 ppm (s) and 2.36 ppm (s). $J_{\text{SCH}_3, 4\text{H}}$ = 1.0 Hz. [Found: m/e 190, C 44.10; H 5.27; S 50.47. Calc. for C₇H₁₀S₃ (190.35): C 44.17; H 5.30; S 50.53.]

3-Bromo-5-methyl-3-thiophenecarboxylic acid (125). To 24.0 g (0.237 mol) of diisopropyl amine in 100 ml of ether, 160 ml (0.240 mol) of 1.50 M butyllithium in hexane was added. After 10 minutes, 35.4 g (0.200 mol) of 4-bromo-2-methylthiophene (121) in 100 ml of ether was added rapidly at room temperature. The reaction mixture was poured onto solid carbon dioxide in ether after 45 min and extracted with aq. 2 N NaOH. Upon acidification with 5 N HCl, 29.1 g (56 %) of the title compound was isolated, which was sufficiently pure to use in synthetic work according to nmr. Recrystallization from ethanol:water gave the pure acid, m.p. 205-206°C. Nmr (acetone-d₆): $\delta_{4\text{H}}$ = 6.93 ppm (q, 1H); δ_{SCH_3} = 2.53 ppm (d, 3H); δ_{COOH} = 9.10 ppm. $J_{\text{SCH}_3, 4\text{H}}$ = 1.0

Hz. [Found: C 32.63; H 2.30; S 14.55. Calc. for $C_6H_5BrO_2S$ (221.07): C 32.60; H 2.30; S 14.50.]

3-Bromo-5,N,N-trimethyl-2-thiophenecarboxamide (126). To a solution of 17.9 g (0.150 mol) of thionyl chloride in 50 ml of ether, 22.1 g (0.100 mol) of 3-bromo-5-methyl-2-thiophenecarboxylic acid (125) was added in portions, followed by 2 ml of pyridine. The mixture was refluxed with stirring for 2.5 h, whereupon the solvent, together with the excess of thionyl chloride, was evaporated. The residue (white needles) was dissolved in 100 ml of anhydrous benzene and dimethylamine was led through the reaction mixture (ice cooling). When 20 g of dimethylamine had been introduced, the reaction mixture was filtered and the filter was washed several times with ether. The filtrate was evaporated and the residue dissolved in ether. The organic layer was washed with 2 N HCl, 2 N NaOH, water and dried. After evaporation and distillation, 11.8 g (48 %) of the pure amide was obtained, b.p._{0.5} 128-130°C. Ir: C=O 1630 cm^{-1} . Nmr (CCl_4): $\delta_{4H} = 6.55$ ppm (q, 1H); $\delta_{5CH_3} = 2.45$ ppm (d, 3H); $\delta_{NCH_3} = 2.98$ ppm (s, 6H). $J_{5CH_3, 4H} = 1.1$ Hz. [Found: C 38.75; H 4.05.

Calc. for $C_8H_{10}BrNOS$ (248.14): C 38.72; H 4.06.]

3-Bromo-5,N,N-trimethyl-2-thenylamine (94). To 1.05 g (0.0277 mol) of $LiAlH_4$ in 25 ml of ether, 10.0 g (0.0403 mol) of 3-bromo-5,N,N-trimethyl-2-thiophenecarboxamide (126) in 25 ml of ether was added. When the addition was complete, the reaction mixture was refluxed for 3 h, cooled and 1.0 ml of water was added. The reaction mixture was filtered and the filter was washed with ether. The filtrate was dried over KOH pellets, evaporated and distilled (some decomposition), which gave 5.0 g (53 %) of the title compound, b.p._{0.6} 69-73°C. Nmr (CCl_4): $\delta_{4H} = 6.49$ ppm (q, 1H); $\delta_{5CH_3} = 2.43$ ppm (bs, 3H); $\delta_{2-CH_2-} = 3.47$ ppm (s, 2H); $\delta_{NCH_3} = 2.20$ ppm (s, 6H). $J_{5CH_3, 4H} = 1.0$ Hz. [Found: C 41.12; H 5.14; S 13.65. Calc. for $C_8H_{12}BrNS$ (234.16): C 41.04; H 5.17; S 13.69.]

3,5-Dibromo-2-phenylthiophene¹⁴⁶ (128) was prepared according to Ref. 146 from 38.5 g (0.241 mol) of 2-phenylthiophene in 250 ml of acetic acid and 80 g (0.50 mol) of bromine in 200 ml of acetic acid; yield 51.2 g (67 %) of 128, m.p. 54-56°C after recrystallization from ethanol:acetone (10:1)

(lit.¹⁴⁶ m.p. 55-56°C).

3-Bromo-5-methyl-2-phenylthiophene (48). To 50.0 g (0.157 mol) of 3,5-dibromo-2-phenylthiophene (128) in 250 ml of ether, 115 ml (0.161 mol) of 1.40 M butyllithium in hexane was added at -70°C followed by 20.5 g (0.163 mol) of DMS in 100 ml of ether. The temperature was kept below -65°C. When the addition was complete, the reaction mixture was stirred at -70°C for 4 h, whereupon it was allowed to reach room temperature. Conc. ammonium hydroxide was added and the ethereal layer was washed with 2 N HCl, water and dried. Evaporation and distillation gave 22.3 g (56 %) of the title compound, b.p._{1.0} 116-120°C. Nmr (CCl₄): $\delta_{C_6H_5} = 7.1-7.7$ ppm (m, 5H); $\delta_{4H} = 6.60$ ppm (q, 1H); $\delta_{5CH_3} = 2.33$ ppm (d, 3H). $J_{5CH_3, 4H} = 1.1$ Hz. [Found: C 52.12; H 3.60; Br 31.60; S 12.61. Calc. for C₁₁H₉BrS (253.16): C 52.19; H 3.58; Br 31.56; S 12.67.]

3-Iodo-5-methyl-2-phenylthiophene (59). To a solution of 8.38 g (0.0331 mol) of 3-bromo-5-methyl-2-phenylthiophene in 100 ml of ether, 25 ml (0.035 mol) of 1.40 M butyllithium in hexane was added at -70°C, followed by 8.9 g (0.035 mol) of iodine in 100 ml of ether. The reaction mixture was allowed to reach room temperature, whereupon it was poured into aq. sodium thiosulphate. The organic layer was washed with water to neutral reaction and dried. Evaporation of the solvent yielded 8.7 g of crude 59, which was distilled to give 5.4 g (54 %) of the title compound, b.p.₁₀₋₃ 118-119°C. Nmr (CCl₄): $\delta_{C_6H_5} = 7.15-7.65$ ppm (m, 5H); $\delta_{4H} = 6.66$ ppm (q, 1H); $\delta_{5CH_3} = 2.38$ ppm (d, 3H). $J_{4H, 5CH_3} = 1.1$ Hz. [Found: C 43.98; H 3.04; S 10.78. Calc. for C₁₁H₉IS (300.16): C 44.02; H 3.02; S 10.68.]

3-Bromo-2-chlorothiophene^{147b} (129) was prepared according to Ref. 147b from 48.9 g (0.300 mol) of 3-bromothiophene and 40.2 g (0.301 mol) of NCS; yield 40 g (68 %), b.p.₁₄ 77-80°C (lit.^{147b} b.p.g 68-72°C).

2-Chloro-3,5-dibromothiophene^{147a} (130). A mixture of 10.6 g (0.0537 mol) of 3-bromo-2-chlorothiophene (129) and 11.0 g (0.0618 mol) of NBS in 100 ml of acetic acid was refluxed for 2.5 h and was then neutralized with NaHCO₃. The aqueous mixture was extracted with ether and the collected ethereal portions were

washed with 1 N NaOH, dried and evaporated. Distillation gave 7.6 g (51 %) of the title compound, b.p.₁₀ 108-110°C (lit.^{147a} b.p.₁₀ 104-108°C).

3-Bromo-2-chloro-5-methylthiophene (65). To 7.0 g (0.025 mol) of 2-chloro-3,5-dibromothiophene (130) in 50 ml of ether, 18 ml (0.026 mol) of 1.42 M butyllithium in hexane was added at -70°C (yellow precipitate), followed by 3.27 g (0.026 mol) of DMS in 25 ml of ether. The mixture was stirred at -70°C for 1.5 h and was then allowed to reach room temperature, whereupon conc. ammonium hydroxide was added. The usual work-up gave 4.5 g (85 %) of the title compound after distillation, b.p.₁₀ 89-91°C. Nmr (CCl₄): $\delta_{4H} = 6.50$ ppm (q, 1H); $\delta_{5CH_3} = 2.40$ ppm (d, 3H). $J_{5CH_3, 4H} = 1.1$ Hz. [Found: C 28.40; H 2.00; S 15.10. Calc. for C₅H₄BrClS (211.51): C 28.39; H 1.91; S 15.16.]

3-Bromo-2-ethyl-5-methylthiophene⁶¹ (16) was prepared as described in Ref. 61 in 45 % overall yield, starting from 2-ethylthiophene (131), b.p.₁₂ 93-95°C (lit.⁶¹ b.p.₉ 85-87°C).

3-Bromo-2-t-butyl-5-methylthiophene⁶¹ (25) was prepared as described in Ref. 61 in 37 % overall yield, starting from 2-t-butylthiophene (137), b.p.₁₂ 117-122°C (lit.⁶¹ b.p.₉ 104-107°C).

2-Ethyl-5-selenophenylaldehyde (134). To 20.0 g (0.126 mol) of 2-ethylselenophene¹⁸¹ (132) in 100 ml of ether, 80 ml (0.13 mol) of 1.60 M butyllithium in hexane was added at such a rate that gentle reflux was maintained. After the addition, the reaction mixture was cooled to 0°C and 9.5 g (0.13 mol) of DMF in 25 ml of ether was added. The mixture was allowed to reach room temperature and poured onto ice/conc. HCl. The aqueous layer was extracted with ether and the collected ethereal phases were washed with water, dried and evaporated, leaving 19.9 g of crude product. Distillation gave 15.0 g (64 %) of the title compound, b.p.₁₁ 121-123°C. Nmr (CCl₄): $\delta_{3H} = 7.75$ ppm (d, 1H); $\delta_{4H} = 7.05$ ppm (d, t, 1H); $\delta_{C_2H_5} = 2.93$ ppm (bq, 2H) and 1.33 ppm (t, 3H); $\delta_{CHO} = 9.58$ ppm (s, 1H). $J_{3H, 4H} = 4.0$ Hz; $J_{4H, 5-CH_2} = 1.1$ Hz. [Found: C 44.80; H 4.52; Se 42.04. Calc. for C₇H₈OSe (187.10): C 44.94; H 4.31; Se 42.20.]

3-Bromo-2-ethyl-5-selenophenylaldehyde (136) was prepared

in a way analogous to that used for the corresponding thiophene derivative 135 (Ref. 61), from 14.0 g (0.0748 mol) of 2-ethyl-5-selenophenylaldehyde (134), 25.0 g (0.187 mol) of dry AlCl_3 and 13 g (0.081 mol) of bromine. After distillation, 12.6 g (63 %) of the title compound was obtained, b.p. $113-115^\circ\text{C}$. Nmr (CCl_4): $\delta_{4\text{H}} = 7.77$ ppm (s, 1H); $\delta_{2\text{C}_2\text{H}_5} = 2.84$ ppm (q, 2H) and 1.32 ppm (t, 3H); $\delta_{\text{CHO}} = 9.60$ ppm (s, 1H). $J_{\text{CH}_2-\text{CH}_3} = 7.0$ Hz. [Found: C 31.61; H 2.65; Se 29.69. Calc. for $\text{C}_7\text{H}_7\text{BrSe}$ (266.00): C 31.61; H 2.65; Se 29.68.]

3-Bromo-2-ethyl-5-methylselenophene (12). A mixture of 10.0 g (0.0376 mol) of 3-bromo-2-ethyl-5-selenophenylaldehyde (136), 6 ml of 99.5 % hydrazine hydrate and 30 ml of ethylene glycol was heated gradually to 140°C , during which time water and hydrazine were distilled off. After cooling to room temperature, 6.0 g of KOH pellets was added, and the mixture was heated to $90-116^\circ\text{C}$. The solution became red and was kept at 116°C for 2.5 h, until nitrogen formation had subsided. After steam distillation, extraction of the distillate with ether, drying and evaporation of the solvent 6.0 g of crude 12 remained. Distillation gave 5.0 g (53 %) of the pure title compound, b.p. $99-102^\circ\text{C}$. Nmr (CCl_4): $\delta_{4\text{H}} = 6.65$ ppm (q, 1H); $\delta_{5\text{CH}_3} = 2.46$ ppm (m, 3H); $\delta_{\text{C}_2\text{H}_5} = 2.73$ ppm (q, 2H) and 1.22 ppm (t, 3H). $J_{4\text{H}, 5\text{CH}_3} = 1.3$ Hz; $J_{\text{CH}_2-\text{CH}_3} = 7.0$ Hz. [Found: C 33.34; H 3.69; Se 31.38. Calc. for $\text{C}_7\text{H}_9\text{BrSe}$ (252.01): C 33.36; H 3.60; Se 31.33.]

2-t-Butyl-3-iodo-5-methylthiophene (110). A solution of 2.1 g (9.0 mmol) of 3-bromo-2-t-butyl-5-methylthiophene (25) in 50 ml of ether was cooled to -70°C and 7.1 ml (9.9 mmol) of 1.40 M butyllithium in hexane was added, followed by 2.6 g (10 mmol) of iodine dissolved in 50 ml of ether. The mixture was allowed to reach room temperature, whereupon it was poured into aqueous sodium thiosulphate. The ethereal layer was separated and the aqueous phase was extracted with ether. The collected ether portions were washed with water and dried. Evaporation of the solvent and distillation gave 1.9 g (75 %) of the title compound, b.p. $95-97^\circ\text{C}$. Nmr (CCl_4): $\delta_{\text{C}(\text{CH}_3)_3} =$

1.47 ppm (s, 9H); $\delta_{5\text{CH}_3} = 2.35$ ppm (d, 3H); $\delta_{4\text{H}} = 6.60$ ppm (q, 1H). $J_{4\text{H}, 5\text{CH}_3} = 1.0$ Hz. [Found: C 38.70; H 4.71; S 11.50. Calc. for $\text{C}_9\text{H}_{13}\text{S}$ (280.17): C 38.58; H 4.68; S 11.44.]

3-Acetyl-2-ethyl-5-methylthiophene (167). A solution of 10.2 g (49.7 mmol) of 3-bromo-2-ethyl-5-methylthiophene (16) in 100 ml of ether was cooled to -70°C , and 42 ml (55 mmol) of 1.30 M butyllithium in hexane was added. The mixture was stirred for 1 h at this temperature, whereupon 4.8 g (55 mmol) of DMA in 50 ml of ether was added. The reaction mixture was allowed to reach room temperature, stirred overnight and poured into 5 N HCl/ice. After stirring for 1 h, the aqueous layer was extracted with ether and the ethereal portions were washed with water and dried. Evaporation of the solvent and distillation gave 3.5 g (42 %) of the title compound, b.p._{0.6} $60-65^\circ\text{C}$. Nmr (CCl_4): $\delta_{4\text{H}} = 6.90$ ppm (q, 1H); $\delta_{\text{COCH}_3} = 2.33$ ppm (s); $\delta_{5\text{CH}_3} = 2.40$ ppm (bs); $\delta_{2\text{C}_2\text{H}_5} = 3.08$ ppm (q, 2H) and 1.25 ppm (t, 3H). $J_{4\text{H}, 5\text{CH}_3} = 1.0$ Hz; $J_{\text{CH}_2-\text{CH}_3} = 7.0$ Hz. [Found: C 63.5; H 7.34; S 19.0. Calc. for $\text{C}_9\text{H}_{12}\text{OS}$ (168.26): C 64.25; H 7.19; S 19.06.]

2,3-Diethyl-5-methylthiophene (168). A mixture of 3.5 g (21 mmol) of 3-acetyl-2-ethyl-5-methylthiophene (167) and 5 ml of 99.5 % hydrazine hydrate in 20 ml of ethylene glycol was gradually heated to 140°C . Water and hydrazine were distilled off. After cooling, 5 g of KOH pellets was added and the mixture was heated to $90-110^\circ\text{C}$ until the nitrogen evolution ceased (2 h), whereupon the mixture was cooled and poured into 200 ml of 2 N HCl and extracted with ether. The ethereal portions were washed with water and dried. Evaporation and distillation gave 0.6 g (19 %) of the title compound, b.p.₁₂ $94-96^\circ\text{C}$. Mass spectrum: $m/e = 154$, 35 % (M^+); $m/e = 139$, 100 % ($[\text{M}-15]^+$). Nmr (CCl_4): $\delta_{4\text{H}} = 6.32$ ppm (q, 1H); $\delta_{5\text{CH}_3} = 2.33$ ppm (d); $\delta_{\text{C}_2\text{H}_5} = 2.2-2.8$ and 0.9-1.4 ppm. $J_{4\text{H}, 5\text{CH}_3} = 1.4$ Hz. [Found: C 70.13; H 9.05; S 20.65. Calc. for $\text{C}_9\text{H}_{14}\text{S}$ (154.28): C 70.07; H 9.15; S 20.78.]

2-Methoxy-5-methylthiophene⁴⁸ (142) was prepared as described in Ref. 48 (for the preparation of 2-methoxythiophene) from 44.8 g (0.200 mol) of 2-iodo-5-methylthiophene¹⁰⁹ (140), 16 g (0.20 mol) of cupric oxide and 0.600 mol of sodium methylate

(from 13.8 g (0.600 mol) of sodium and 220 g of methanol). After 6 days, 10 % of the starting material remained. After work-up and distillation, 13.9 g (54 %) of the title compound was obtained, b.p.₁₂ 58-60°C (lit.⁴⁸ b.p.₁₀ 51-52°C).

2-Methoxy-5-methylselenophene¹⁵³ (143). To a mixture of 25 ml of dry HMPA and 9 ml of methanol, 1.3 g (0.057 mol) of sodium was added. When all of the sodium was consumed, the methanol was evaporated at 10 mm Hg, and 5.00 g (0.0185 mol) of 2-iodo-5-methylselenophene (141), together with 2.0 g of cupric oxide, were added. After 48 h at room temperature, the starting material was consumed as shown by vpc (column SE 30, 3 %, 100-200°C, 10°/min) on a hydrolyzed sample. The reaction mixture was poured into water and extracted with ether. The ethereal phase was washed with water and dried. Evaporation and distillation gave 1.53 g (47 %) of the title compound, b.p.₁₂ 73-76°C. The nmr spectrum (CCl₄) was identical with that of an authentic sample.¹⁵³ When the same method as for the preparation of 142 was used, only a 23 % yield was obtained. Extensive decomposition took place during the reaction, which was evident from the formation of red selenium.

2-Iodo-5-methylselenophene (141). To a mixture of 43.5 g (0.300 mol) of 2-methylselenophene (146) in 300 ml of CCl₄, 200 ml of acetic acid, 300 ml of water and 2.0 ml of conc. H₂SO₄ was added, followed by 30.0 g (0.118 mol) of iodine and 12.3 g (0.0700 mol) of iodic acid dissolved in water. The latter two reagents were added in portions. This mixture was stirred vigorously at room temperature for 4 h, whereupon it was poured into aqueous sodium thiosulphate and extracted with CCl₄. The organic phases were washed with 1 N NaOH, water and dried. Evaporation and distillation gave 65.7 g (81 %) of the title compound, b.p._{0.6} 59-60°C. Nmr (CCl₄): $\delta_{3H} = 7.15$ ppm (d, 1H); $\delta_{4H} = 6.42$ ppm (d, q, 1H); $\delta_{5CH_3} = 2.50$ ppm (d, 3H). $J_{3H,4H} = 3.6$ Hz; $J_{4H,5CH_3} = 1.2$ Hz; $J_{Se,5CH_3} = 9.6$ Hz. [Found: C 22.21; H 1.88; Se 29.21. Calc. for C₅H₅ISe (270.96): C 22.16; H 1.86; Se 29.14.]

3-Bromo-2-methoxy-5-methylthiophene (64). To 12.8 g (0.100 mol) of 2-methoxy-5-methylthiophene (142) in 100 ml of acetic acid, 19.6 g (0.110 mol) of NBS was added in portions at +17°C (ice cooling). When the addition was complete, the mixture

was stirred for 1/2 h, whereupon it was poured into water. The aqueous phase was neutralized with NaHCO_3 and extracted with ether. The ethereal phase was filtered through alumina (Brockm. I, neutral) in order to remove some black solid material, and dried. Evaporation and distillation gave 7.0 g (34 %) of the title compound, b.p.₂₀ 115-117°C (decomp.). The substance darkened rapidly at room temperature, and even at -25°C in the dark. Nmr (CCl_4): $\delta_{4\text{H}} = 6.31$ ppm (q, 1H); $\delta_{5\text{CH}_3} = 2.32$ ppm (d, 3H); $\delta_{\text{OCH}_3} = 3.83$ ppm (s, 3H). $J_{4\text{H}, 5\text{CH}_3} = 1.2$ Hz. [Found: C 34.8; H 3.46; S 15.0. Calc. for $\text{C}_6\text{H}_7\text{BrOS}$ (207.09): C 34.80; H 3.41; S 15.48.]

Attempted preparation of 3-bromo-2-methoxy-5-methylselenophene (144). When 2-methoxy-5-methylselenophene (143) was treated with NBS as in the preceding experiment, only black, unidentified material was formed immediately upon the NBS addition.

3,5-Dibromo-2-methylthiophene¹⁷⁴ (147) was prepared according to Ref. 83 (except that chloroform was replaced by acetic acid in 63 % yield, from 19.6 g (0.200 mol) of 2-methylthiophene (145) in 150 ml of acetic acid and 66 g (0.41 mol) of bromine in 50 ml of acetic acid; b.p.₁₀ 102-104°C (32.2 g) (lit.⁸³ b.p.₁₀ 98.5-100°C).

3,5-Dibromo-2-methylselenophene (148).

a) To a stirred solution of 9.6 g (0.066 mol) of 2-methylselenophene (146) in 70 ml of acetic acid, 25.8 g (0.145 mol) of NBS was added in portions at room temperature. When the addition was complete, the solution was stirred for 30 min and poured into water. This mixture was extracted several times with ether and the combined ethereal phases were washed with aq. NaHCO_3 and water to neutral reaction. The ethereal phase was dried and fractionated to yield 11.0 g (55 %) of the title compound, b.p.₁ 81-82°C. Nmr (CCl_4): $\delta_{2\text{CH}_3} = 2.32$ ppm (s, 3H); $\delta_{4\text{H}} = 6.98$ ppm (s, 1H). [Found: C 19.86; H 1.28; Br 52.87; Se 26.07. Calc. for $\text{C}_5\text{H}_4\text{Br}_2\text{Se}$ (302.86): C 19.83; H 1.33; Br 52.77; Se 26.07.]

Black tar resulted when 146 was treated with bromine as in the thiophene case.

b) To a solution of 7.0 g (0.048 mol) of 146 in 50 ml of carbon disulphide, 16 g (0.10 mol) of bromine in 20 ml of acetic acid was added at -30°C . When the addition was complete, the mixture was stirred at room temperature overnight and then poured into water and worked up as above. Evaporation of the solvent gave 16.8 g of a brown fuming oil, which reacted violently with solid KOH. After the base treatment, the residue was distilled, giving 6.0 g (41 %) of the title compound.

c) To a solution of 11.2 g (0.0500 mol) of 2-bromo-5-methylselenophene (150) in 50 ml of acetic acid, 8.0 g (0.050 mol) of bromine in 25 ml of acetic acid was added at room temperature. The mixture was stirred for 1.5 h and then poured into water. The aqueous phase was neutralized with dil. aq. NaOH and extracted with ether. The ethereal portions were dried and the solvent evaporated, giving 12.9 g of a crude product which was distilled to yield 8.0 g (53 %) of the title compound.

2,5-Dibromoselenophene^{80a} (149). To a solution of 50.0 g (0.382 mol) of selenophene in 50 ml of acetic acid, 126 g (0.788 mol) of bromine in 80 ml of acetic acid was added (ice cooling). After stirring overnight the reaction mixture was poured into water and worked up as mentioned previously (see compound 147). Distillation gave 77.7 g (70 %) of the title compound, b.p.₁₃ $101-104^{\circ}\text{C}$, n_{D}^{20} 1.6665 (lit.^{80a} b.p._{0.02} 42°C , n_{D}^{20} 1.667).

2-Bromo-5-methylselenophene (150). To a solution of 28.9 g (0.100 mol) of 2,5-dibromoselenophene (149) in 200 ml of ether, 65 ml (0.10 mol) of 1.60 M butyllithium in hexane was added at -50°C , followed by 13.0 g (0.103 mol) of DMS in 50 ml of ether at -30°C . The reaction mixture was allowed to reach room temperature and was kept there for 1 h, whereupon conc. ammonium hydroxide was added. The usual work-up, evaporation and distillation gave 15.0 g (67 %) of the title compound, b.p.₁₁ $79-80^{\circ}\text{C}$. Nmr (CCl_4): $\delta_{3\text{H}}$ = 6.90 ppm (d, 1H); $\delta_{4\text{H}}$ = 6.52 ppm (d, q, 1H); $\delta_{5\text{CH}_3}$ = 2.46 ppm (d, 3H). $J_{3\text{H},4\text{H}}$ = 3.8 Hz; $J_{4\text{H},5\text{CH}_3}$ = 1.2 Hz. [Found: C 26.75; H 2.28; Br 35.66; Se 35.20. Calc. for $\text{C}_5\text{H}_5\text{BrSe}$ (223.96): C 26.82; H 2.25; Br 35.68; Se 35.26.]

3-Bromo-2-methyl-5-thiophenecarboxylic acid (151). To 46.3 g (0.181 mol) of 3,5-dibromo-2-methylthiophene (147) in

200 ml of ether, 140 ml (0.186 mol) of 1.33 M butyllithium in ether was added at -70°C . The mixture was stirred for 20 min, whereupon it was poured onto solid carbon dioxide in ether. The ethereal phase was extracted with 2 N NaOH and the alkaline portions were acidified with 5 N HCl, which gave 35.2 g of the crude acid. Recrystallization from acetic acid:water gave the pure title compound, m.p. $197-200^{\circ}\text{C}$, 30.2 g (75 %). Nmr (acetone- d_6): $\delta_{4\text{H}} = 7.60$ ppm (s,1H); $\delta_{2\text{CH}_3} = 2.47$ ppm (s,3H). [Found: C 32.70; H 2.30; Br 36.09; S 14.52. Calc. for $\text{C}_6\text{H}_5\text{BrO}_2\text{S}$ (221.07): C 32.60; H 2.28; Br 36.14; S 14.50.]

3-Bromo-2-methyl-5-phenylthiophene (56). To 25.6 g (0.100 mol) of 3,5-dibromo-2-methylthiophene (147) in 250 ml of ether, 100 ml (0.110 mol) of 1.10 M butyllithium in hexane was added at -70°C . After 0.5 h 10.0 g (0.102 mol) of cyclohexanone in 100 ml of ether was added and the mixture was allowed to reach room temperature, whereupon 100 ml of 5 N HCl was added. After stirring for 0.5 h the ethereal layer was washed with water and dried. Evaporation yielded 25.0 g of crude 3-bromo-5-(-1-cyclohexenyl)-2-methylthiophene (152), which was aromatized with 40 g (0.18 mol) of DDQ in 400 ml of refluxing benzene for 2.5 h. The mixture was cooled and filtered and the filter was washed with benzene several times. The filtrate was washed repeatedly with 5 N NaOH solution and finally with water. Evaporation of the solvent and recrystallization from ethanol:water yielded 12.9 g (51 %) of the title compound, m.p. $72-73^{\circ}\text{C}$. Nmr (CCl_4): $\delta_{4\text{H}} = 7.00$ ppm (s,1H); $\delta_{\text{C}_6\text{H}_5} = 7.1-7.6$ ppm (m,5H); $\delta_{2\text{CH}_3} = 2.37$ ppm (s,3H). [Found: C 52.16; H 3.51; Br 31.57; S 12.71. Calc. for $\text{C}_{11}\text{H}_9\text{BrS}$ (253.16): C 52.19; H 3.58; Br 31.56; S 12.67.]

3-Iodo-2-methyl-5-phenylthiophene (61) was prepared in a way analogous to that used for the isomeric 4-halo-2-methyl derivative 59, from 3.00 g (0.0119 mol) of 3-bromo-2-methyl-5-phenylthiophene (56) in 75 ml of ether, 10 ml (0.012 mol) of 1.20 M butyllithium in hexane and 3.2 g (0.013 mol) of iodine dissolved in 75 ml of ether. Thus 3.56 g of a crystalline crude product was obtained, which was recrystallized from ethanol to give the title compound, m.p. $65-66^{\circ}\text{C}$, 2.16 g (60 %). Nmr (CCl_4): $\delta_{\text{C}_6\text{H}_5} = 7.1-7.6$ ppm (m,5H); $\delta_{4\text{H}} = 7.08$ ppm (s,1H); $\delta_{2\text{CH}_3} = 2.45$ ppm (s,3H). [Found: C 44.1; H 2.99; I 41.8. Calc. for $\text{C}_{11}\text{H}_9\text{IS}$

(300.16): C 44.02; H 3.02; I 42.28.]

3-Bromo-5-methoxy-2-methylthiophene (76). To a solution of 28.6 g (0.112 mol) of 3,5-dibromo-2-methylthiophene (147) in 150 ml of ether, 68 ml (0.12 mol) of 1.69 M butyllithium in hexane was added at -70°C , followed by 27 g (0.12 mol) of tri-butylborate after 15 min. The reaction temperature was allowed to rise to -10°C during 1 h, whereupon 14 ml (0.12 mol) of 30 % hydrogen peroxide was added. The mixture was refluxed for 1 h and then poured into water. The alkaline aqueous layer was extracted with 50 ml of ether and acidified with 1 N HCl. The acidic aqueous solution was extracted with ether and the ethereal portions were dried. Evaporation of the solvent gave 18.7 g of the crude "hydroxythiophene" 153; $\text{ir: C=O } 1695 \text{ cm}^{-1}$. This crude product (~ 0.10 mol), and 25 g (0.20 mol) of DMS, were dissolved in 100 ml of CHCl_3 and a mixture of 33.0 g (0.097 mol) of TBA, 8.0 g (0.20 mol) of NaOH and 97 ml of water was added with stirring (ice cooling). When the addition was complete, the mixture was stirred for 1 h, whereupon the organic layer was separated, washed with water and dried. Evaporation of the solvent and distillation yielded 7.5 g (32 %) of the title compound, b.p._{0.7} $57-61^{\circ}\text{C}$. Nmr (CCl_4): $\delta_{4\text{H}} = 5.88 \text{ ppm (s, 1H)}$; $\delta_{2\text{CH}_3} = 2.23 \text{ ppm (s, 3H)}$; $\delta_{\text{OCH}_3} = 3.77 \text{ ppm (s, 3H)}$. [Found: C 34.96; H 3.49; S 15.40. Calc. for $\text{C}_6\text{H}_7\text{BrOS}$ (207.09): C 34.80; H 3.41; S 15.48.]

3-Bromo-2-methyl-5-methylthioselenophene (92). To a stirred solution of 7.74 g (0.0256 mol) of 3,5-dibromo-2-methylselenophene (148) in 50 ml of ether, 16 ml (0.026 mol) of 1.60 M butyllithium in hexane was added at -70°C . After 10 min the reaction mixture was pressed (with nitrogen) into 2.45 g (0.0261 mol) of dimethyldisulphide in 25 ml of ether (cf. Ref. 145). This mixture was stirred for 3 h and then hydrolyzed with water. The ether phase was washed with dilute sodium hydroxide solution and water, dried and fractionated to yield 4.42 g (64 %) of the title compound, b.p._{0.8} $89-93^{\circ}\text{C}$. Nmr (CCl_4): $\delta_{\text{SCH}_3} = 2.42 \text{ ppm (s)}$; $\delta_{2\text{CH}_3} = 2.37 \text{ ppm (d)}$; $\delta_{4\text{H}} = 7.95 \text{ ppm (bs)}$. The splitting of the 2CH_3 signal = 0.5 Hz. [Found: C 26.60; H 2.55; Br 29.56; S 11.78; Se 29.40. Calc. for $\text{C}_6\text{H}_7\text{BrSSe}$ (270.05): C 26.69; H 2.61; Br 29.59; S 11.87; Se 29.24.]

3-Bromo-2-methyl-5-methylthiophene (88). From 36.0 g (0.141 mol) of 3,5-dibromo-2-methylthiophene (147) in 100 ml of ether, 94 ml (0.15 mol) of 1.60 M butyllithium in hexane and 14.1 g (0.150 mol) of dimethyldisulphide, 22.2 g (71 %) of the title compound, b.p._{1.4} 79-81°C was obtained, following the procedure described above. Nmr (CCl₄): δ_{SCH_3} , δ_{CH_3} = 2.29 ppm (s) and 2.36 ppm (s), (integral = 6H); $\delta_{4\text{H}}$ = 6.78 ppm (s, 1H). [Found: C 32.22; H 3.19; Br 35.80; S 28.80. Calc. for C₆H₇BrS₂ (223.15): C 32.29; H 3.16; Br 35.81; S 28.71.]

3-Bromo-2,N,N-trimethyl-5-thiophenecarboxamide (91) was prepared in analogy with its isomer (126) from 35.2 g (0.159 mol) of 3-bromo-2-methyl-5-thiophenecarboxylic acid (151), in 250 ml of ether, 23.8 g (0.200 mol) of thionyl chloride and 2 ml of pyridine. The crude acid chloride was dissolved in 250 ml of benzene and 15 g of dimethylamine was bubbled through the mixture. After work-up and distillation, 29.0 g (74 %) of the title compound was obtained; b.p.₁ 144-145°C. Ir: C=O 1625 cm⁻¹. Nmr (CCl₄): $\delta_{4\text{H}}$ = 7.08 ppm (s, 1H); $\delta_{2\text{CH}_3}$ = 2.38 ppm (s, 3H); δ_{NCH_3} = 3.10 ppm (s, 6H). [Found: C 38.80; H 4.11; S 12.85. Calc. for C₈H₁₀BrNOS (248.14): C 38.72; H 4.06; S 12.92.]

3-Bromo-2,N,N-trimethyl-5-thenylamine (95) was prepared in analogy with its isomer (94) from 27.2 g (0.110 mol) of 3-bromo-2,N,N-trimethyl-5-thiophenecarboxamide (91) and 2.5 g (0.066 mol) of LiAlH₄ in 150 ml of ether; yield 18.7 g (73 %), b.p._{1.0} 85-87°C. Nmr (CCl₄): $\delta_{4\text{H}}$ = 6.65 ppm (s, 1H); $\delta_{5\text{-CH}_2\text{-}}$ = 3.47 ppm (s, 2H); $\delta_{2\text{CH}_3}$ = 2.37 ppm (s, 3H); δ_{NCH_3} = 2.20 ppm (s, 6H). [Found: C 41.00; H 5.20; S 13.75. Calc. for C₈H₁₂BrNS (234.16): C 41.04; H 5.17; S 13.69.]

3-Bromo-5-chloro-2-methylthiophene (77) was prepared in analogy with its isomer ^{147a}65 from 14.8 g (0.0536 mol) of 2,3-dibromo-5-chlorothiophene (154) in 100 ml of ether, 40 ml (0.057 mol) of 1.42 M butyllithium in hexane and 7.56 g (0.0600 mol) of DMS in 50 ml of ether; yield 7.7 g (68 %), b.p.₁₀ 84-85°C. Nmr (CCl₄): $\delta_{4\text{H}}$ = 6.67 ppm (s, 1H); $\delta_{2\text{CH}_3}$ = 2.32 ppm (s, 3H). [Found: C 28.34; H 1.95; S 15.17. Calc. for C₅H₄BrClS (211.51): C 28.39; H 1.91; S 15.16.]

5-Acetyl-3-bromo-2-methylthiophene⁶¹ (157) was prepared according to Ref. 61 from 35.0 g (0.250 mol) of 2-acetyl-5-methylthiophene¹⁸³ (155), 85 g (0.64 mol) of dry AlCl₃ and 43 g (0.27 mol) of bromine. Yield: 38.2 g (70 %), b.p.₁₁ 142-148°C (lit.⁶¹ b.p.₁₅ 140-144°C, 71 %).

2-Acetyl-5-methylselenophene¹⁵⁸ (156). A mixture of 25.0 g (0.172 mol) of 2-methylselenophene,¹²⁷ 40 g (0.39 mol) of acetic anhydride and 8 drops of perchloric acid (70 %) was refluxed for 1 h, cooled and poured into ice-water. The aqueous phase was extracted with ether and the ethereal portions were dried. Evaporation and distillation yielded 16.5 g (51 %) of the title compound, b.p.₁₃ 122-124°C (lit.¹⁵⁸ b.p.₁₂ 114-116°C). Nmr (CCl₄): $\delta_{3H} = 7.61$ ppm (d,d,1H); $\delta_{4H} = 6.90$ ppm (d,q,1H); $\delta_{5CH_3} = 2.55$ ppm (d,d,3H); $\delta_{COCH_3} = 2.39$ ppm (s,3H). $J_{3H,4H} = 3.6$ Hz; $J_{4H,5CH_3} = 1.0$ Hz; $J_{3H,5CH_3} = 0.4$ Hz.

5-Acetyl-3-bromo-2-methylselenophene (158) was prepared with the procedure used for the synthesis of 157 (Ref. 61) from 18.7 g (0.100 mol) of 2-acetyl-5-methylselenophene¹⁵⁸ (156), 33 g (0.25 mol) of AlCl₃ and 19.2 g (0.120 mol) of bromine; yield: 18.4 g (69 %), b.p._{1.4} 108-111°C. Nmr (CCl₄): $\delta_{4H} = 7.60$ ppm (bs,1H); $\delta_{2CH_3}, \delta_{COCH_3} = 2.45$ ppm (bs). The integral of the methyl band represented 6H. [Found: C 31.57; H 2.70; Se 29.67. Calc. for C₇H₇BrOSe (266.00): C 31.61; H 2.65; Se 29.69.]

3-Bromo-5-ethyl-2-methylthiophene⁶¹ (21) was prepared according to Ref. 61 from 25.0 g (0.114 mol) of 5-acetyl-3-bromo-2-methylthiophene (157), 100 ml of ethylene glycol, 25 ml of 99.5 % hydrazine hydrate and 25 g of potassium hydroxide; yield 18.2 g (78 %). B.p.₁₀ 85-87°C (lit.⁶¹ b.p.₁₃ 89-91°C).

3-Bromo-5-ethyl-2-methylselenophene (13).

a) A solution of 9.10 g (0.0300 mol) of 3,5-dibromo-2-methylselenophene (148) in 150 ml of ether was cooled to -70°C and 20 ml (0.030 mol) of 1.50 M butyllithium in hexane was added dropwise, followed by 9.25 g (0.0600 mol) of diethylsulphate in 25 ml of ether after 10 minutes. The reaction mixture was slowly heated and an exothermic reaction took place at +17 - +25°C, after which it was left overnight. Conc. ammonium hydroxide was added and the mixture was stirred for 1 h. The

ethereal layer was separated, washed with 2 N HCl, water and dried. Evaporation and distillation gave 2.8 g (37 %) of almost pure title compound, b.p.₁₂ 101-104°C. Vpc and nmr analysis showed that some diethyl sulphate (~ 10 %) was present. Repeated distillation and preparative tlc (1 mm silica gel:hexane) did not remove this impurity nor did prolonged treatment with ammonium hydroxide. Nmr (CCl₄): $\delta_{4H} = 6.66$ ppm (bt,1H); $\delta_{2CH_3} = 2.40$ ppm (bs,3H); $\delta_{5C_2H_5} = 2.79$ ppm (q,2H) and 1.25 ppm (t,3H). $J_{CH_2-CH_3} = 7.5$ Hz. [Found: C 34.89; H 3.72; Se 30.66. Calc. for C₇H₉BrSe (252.00): C 33.66; H 3.60; Se 31.33.]

b) When the procedure used for the preparation of 21 was applied on 158, yellow crystals were formed but no trace of the title compound was found. (When the reaction mixture was heated with potassium hydroxide gradually to 170-180°C, red selenium was formed, but no nitrogen evolution was noticed.) The crystals were collected by suction and recrystallized from ethanol twice, but the melting interval was unchanged; 100-105°C. Ir: N-H 3320, 3180 cm⁻¹. M/e = 280; calc. for the hydrazone of 158 (C₇H₉⁷⁹BrN₂⁸⁰Se) = 280. Nmr (CCl₄): $\delta_{4H} = 6.88$ ppm (s,1H); $\delta_{CH_3} = 2.36$ ppm (s,3H) and 2.00 ppm (s,3H); $\delta_{NH_2} = 5.11$ ppm (2H).

c) The tosylhydrazone of 158 was prepared according to a procedure described in Ref. 73, from 2.66 g (0.0100 mol) of 158 and 2.80 g (0.0150 mol) of tosylhydrazine in 50 ml of methanol; yield 3.4 g (78 %), m.p. 191-193°C from methanol in the cold (-25°C). [Found: C 38.4; H 3.54; N 6.78. Calc. for C₁₄H₁₅BrN₂O₂SSe (434.23): C 38.72; H 3.48; N 6.45.]

The tosylhydrazone, 3.0 g (0.0069 mol) was treated with 2.7 g (0.071 mol) of LiAlH₄ in 50 ml of refluxing THF for 18 h (cf. Ref. 73). Upon hydrolysis of the reaction mixture with moist ether, red selenium precipitated and 0.3 g of a brown, uncharacterized oil remained after work-up and evaporation.

5-Acetyl-2-methyl-3-thiophenecarboxylic acid (160).

5-Acetyl-3-bromo-2-methylthiophene (157), 8.67 g (0.0396 mol), was acetalized with 20 ml of ethylene glycol and 0.25 g of p-toluenesulphonic acid in refluxing toluene (150 ml) with water separation (18 h). The reaction mixture was poured onto a

saturated NaHCO_3 solution and washed with water. After drying and evaporation, the residue was distilled, giving the acetal (159) contaminated with $\sim 10\%$ of the starting material according to vpc analysis; b.p.₁ $95-105^\circ\text{C}$, 5.86 g (56 %). The acetal, 5.26 g (0.0200 mol), was dissolved in 50 ml of ether and cooled to -70°C , after which 16 ml (0.020 mol) of 1.25 M butyllithium in hexane was added dropwise. When the addition was complete, the reaction temperature was allowed to rise to -30°C (the warming-up took $\sim 1/2$ h), and the reaction mixture was poured onto solid carbon dioxide in ether. The organic layer was extracted with 3×50 ml of 2 N NaOH solution. The aqueous layer was acidified with conc. HCl and heated to boiling. After filtration, the solution was left overnight at room temperature, whereupon 1.3 g of white crystals was filtered off and the filtrate was evaporated to half of its volume, which gave another 1.5 g of the acid; yield 76 %. Recrystallization from water gave the pure acid, m.p. $167-168^\circ\text{C}$. Nmr ($\text{DMSO}-d_6$): $\delta_{4\text{H}} = 8.03$ ppm (s, 1H); $\delta_{2\text{CH}_3}$, $\delta_{\text{COCH}_3} = 2.53$ ppm (s, 3H), 2.72 ppm (s, 3H). [Found: C 52.7; H 4.35; S 17.5. Calc. for $\text{C}_8\text{H}_8\text{O}_3\text{S}$ (184.21): C 52.16; H 4.38; S 17.41.]

3-Carboxy-2-methyl-5-thienylacetic acid (100). A mixture of 500 mg (2.71 mmol) of 5-acetyl-2-methyl-3-thiophenecarboxylic acid (160), 1.25 g (2.82 mmol) of thallium trinitrate trihydrate and 1.0 ml of perchloric acid (70 %) in 15 ml of methanol was stirred for 18 h at room temperature. The white precipitate (thallium mononitrate) was filtered off and the filtrate diluted with 100 ml of water. The water phase was extracted with 3×30 ml of chloroform and the collected organic portions were extracted with 3×30 ml of 2 N NaOH. The basic water solution was left at room temperature for 1 h and was then acidified. Thus, 280 mg (52 %) of crude 100 was collected, m.p. $\sim 222^\circ\text{C}$. Recrystallization from methanol:water (4:1) gave the pure acid, m.p. $224-226^\circ\text{C}$. Combined vpc-ms (column SE 30, 3 %, $150-200^\circ\text{C}$, $4^\circ/\text{min}$) of the silylated crude product (BSA) showed only one peak (retention time 10.6 min, $m/e = 344$; calc. for the bis-trimethylsilyl ester of 100 ($\text{C}_{14}\text{H}_{24}\text{O}_4\text{SSi}_2$) = 344. Nmr ($\text{DMSO}-d_6$): $\delta_{4\text{H}} = 7.17$ ppm (bs, 1H); $\delta_{2\text{CH}_3} = 2.67$ ppm (s, 3H); $\delta_{2-\text{CH}_2-} = 3.78$ ppm (bs, 2H): Ir: $\text{C}=\text{O}$ 1700 cm^{-1} and 1640 cm^{-1} . The ir spectrum was only

slightly different from that of 3-carboxy-5-methyl-2-thienyl-acetic acid (97). [Found: C 48.4; H 4.12; S 16.0. Calc. for $C_8H_8O_4S$ (200.21): C 48.00; H 4.03; S 16.01.]

An attempt to prepare 3-carboxy-2-methyl-5-thienylacetic acid (100) from 3-bromo-2-methyl-5-thienylacetic acid (116). In 100 ml of THF, 2.1 g (8.9 mmol) of 3-bromo-2-methyl-5-thienylacetic acid (116) was dissolved. The solution was cooled to $-70^{\circ}C$ and 13.6 ml (19.0 mmol) of 1.40 M butyllithium in hexane was added. The reaction mixture was left for 1 h at $-70^{\circ}C$ with stirring, and was then poured onto solid carbon dioxide in ether. The ethereal phase was extracted several times with 2 N NaOH. The combined aqueous phases were acidified with conc. HCl (ice-cooling) and the acidic crude product was taken up in ether, which was evaporated, leaving 2.0 g of a brown oil. Upon treatment with CCl_4 the oil crystallized. The crystals melted between 100 and $120^{\circ}C$ with gas evolution. A sample of the crystals was dissolved in $DMSO-d_6$ and a nmr spectrum recorded, which showed the presence of aromatic protons around $\delta = 6.67$ ppm, methine protons at $\delta = 4.83$ ppm, methylene protons at $\delta = 3.68$ ppm and methyl protons at $\delta = 2.37$ and 2.25 ppm. When the sample was heated slightly ($\sim 45^{\circ}C$), the signal at 4.83 ppm had disappeared and that at $\delta = 3.68$ ppm had increased in height. The methyl signal at $\delta = 2.25$ ppm had also disappeared. These results indicated that a thienyl malonic acid was present, among other compounds.

When the experiment was repeated with 3 eq. of butyllithium, it did not give the desired thienylacetic acid. Instead a great deal of decomposition took place, which did not lead to significant amounts of acidic products.

3-Bromo-2-methyl-5-thienylacetic acid (116). A mixture of 12.3 g (0.0561 mol) of 5-acetyl-3-bromo-2-methylthiophene (157), 27.1 g (0.0610 mol) of thallium trinitrate trihydrate and 28 ml of perchloric acid (70 %) in 140 ml of methanol was stirred at room temperature for 12 h, whereupon the precipitate was filtered off and the filtrate diluted with 300 ml of water. The water phase was extracted with 3x100 ml of chloroform and the collected organic portions were washed with water and dried. Evaporation gave 12.1 g of crude methyl ester, which was dissolved in benzene and chromatographed on an alumina column. Evaporation of the

benzene yielded 9.1 g of a yellow liquid (65 %), which was stirred with 150 ml of 2 N NaOH solution at room temperature for 2 h. The reaction mixture was filtered and acidified with ice-cooled conc. HCl. The crystals were filtered off and washed with 10 ml of ice-water. Thus, 5.2 g of the acid was obtained. Another 0.8 g was obtained from the acidic filtrate through extraction with ether and evaporation; yield 6.0 g, m.p. $\sim 95^{\circ}\text{C}$ (45 % based on 157).

The pure acid was obtained through recrystallization from hexane, m.p. $98-100^{\circ}\text{C}$. Nmr (DMSO- d_6): $\delta_{\text{H}} = 6.78$ ppm (bs, 1H); $\delta_{5\text{-CH}_2-} = 3.73$ ppm (bs, 2H); $\delta_{2\text{CH}_3} = 2.30$ ppm (s, 3H). [Found: C 35.5; H 3.02; S 13.8. Calc. for $\text{C}_7\text{H}_7\text{BrO}_2\text{S}$ (235.10): C 35.76; H 3.00; S 13.64.]

5-t-Butyl-3-iodo-2-methylthiophene⁶¹ (29). From 45.8 g (0.297 mol) of 2-t-butyl-5-methylthiophene¹⁸⁴ (27), 27.9 g (0.110 mol) of iodine, 13.9 g (0.0790 mol) of iodic acid, 150 ml of acetic acid, 60 ml of water, 60 ml of CCl_4 and 2 ml of conc. H_2SO_4 , 84.0 g of a crude product was obtained, following the procedure described in Ref. 61. The product contained 90 % of the title compound and 10 % of its isomer 110 according to combined vpc-ms analysis (column OV 1, 3 %, $100-210^{\circ}\text{C}$, $10^{\circ}/\text{min}$). Distillation gave 64.0 g of material still containing 110, b.p.₁₂ $129-130^{\circ}\text{C}$. To a solution of 60.0 g (0.214 mol) of the distillate in 250 ml of ether, 31 ml (0.043 mol) of 1.40 M butyllithium was added at -70°C . After 30 min the reaction mixture was hydrolyzed with methanol. The usual work-up and distillation gave 35.6 g (43 %) of isomer-free 29, b.p.₁₂ $128-129^{\circ}\text{C}$, $n_{\text{D}}^{20} 1.5704$ (lit.⁶¹ b.p.₁₀ $120-122^{\circ}\text{C}$, $n_{\text{D}}^{20} 1.5715$).

5-t-Butyl-3,4-diiodo-2-methylthiophene (106). A mixture of 15.4 g (0.0998 mol) of 2-t-butyl-5-methylthiophene (27), 20.6 g (0.0811 mol) of iodine, 7.90 g (0.0449 mol) of iodic acid, 40 ml of acetic acid, 15 ml of water, 20 ml of CCl_4 and 1.0 ml of conc. H_2SO_4 was stirred vigorously at 80°C for 8 h and worked up as previously described (see preparation of 1). After distillation 17.3 g (43 %) of the title compound was obtained, b.p._{0.01} $113-123^{\circ}\text{C}$, $n_{\text{D}}^{20} = 1.6430$. Nmr (CCl_4): $\delta_{\text{CH}_3} = 2.48$ ppm (s, 3H); $\delta_{\text{C}(\text{CH}_3)_3} = 1.48$ ppm (s, 9H). [Found: C 26.70; H 3.02; Calc. for $\text{C}_9\text{H}_{12}\text{I}_2\text{S}$ (406.07): C 26.62; H 2.98.]

A fore run, 7.3 g, b.p._{0.01} 65-75°C, was mainly 5-t-butyl-3-iodo-2-methylthiophene (29) (nmr).

Experimental part of Chapter 3.3.4

2,5-Dichlorothiophene¹⁶¹ (161) was prepared according to Ref. 163 and was available in these laboratories.

2,5-Dichloroselenophene^{80a} (74). To a solution of 80.0 g (0.611 mol) of selenophene in 100 ml of dry benzene, 168 g (1.24 mol) of sulphuryl chloride was added during 2 h, whereupon the mixture was refluxed for 6 h. After cooling, the benzene solution was neutralized with NaHCO₃, washed with water and dried. Evaporation of the solvent and distillation gave 56.8 g (46 %) of the title compound, b.p.₁₄ 68-69°C (lit.^{80a} b.p.₁₂ 67°C). Nmr (CCl₄): $\delta_{3H} = 6.74$ ppm (s) (lit.¹²⁹ 6.70 ppm).

2,5-Dichloro-3-iodothiophene^{147a} (69). A mixture of 25.0 g (0.163 mol) of 2,5-dichlorothiophene (161), 14.0 g (0.0551 mol) of iodine, 9.6 g (0.055 mol) of iodic acid, 40 ml of acetic acid, 50 ml of water, 30 ml of CCl₄ and 5 ml of conc. H₂SO₄ was refluxed for 72 h, whereupon it was poured into aqueous sodium thiosulphate and extracted with CCl₄. The collected organic phases were washed with water, dried, and the solvent was evaporated to give a crude product, which was distilled. Thus 31.8 g (70 %) of the title compound was obtained, b.p.₁₅ 123-126°C (lit.^{147a} b.p.₁₁ 112-114°C). Nmr (CCl₄): $\delta_{4H} = 6.69$ ppm (s).

2,5-Dichloro-3-iodoselenophene (71) was prepared as described above from 20.0 g (0.100 mol) of 2,5-dichloroselenophene (74), 8.9 g (0.035 mol) of iodine, 6.2 g (0.035 mol) of iodic acid, 40 ml of acetic acid, 50 ml of water, 30 ml of CCl₄ and 1 ml of conc. H₂SO₄; yield 21.4 g (66 %), b.p._{1.0} 89-93°C. Nmr (CCl₄): $\delta_{4H} = 6.85$ ppm (s). [Found: C 14.85; H 0.40; Se 24.20. Calc. for C₄HCl₂ISE (325.82): C 14.75; H 0.31; Se 24.23.]

2,5-Dichloro-3-methylselenoselenophene (73).

a) A solution of lithium diisopropylamide was prepared from 10.1 g (0.100 mol) of diisopropylamine in 50 ml of ether and 68 ml (0.10 mol) of 1.50 M butyllithium in hexane. This solution was cooled to -70°C and 10.0 g (0.0500 mol) of 2,5-dichloroselenophene (74) in 100 ml of ether was added at such a rate that

the temperature did not exceed -65°C . After the addition, the reaction mixture was stirred at -70°C for 4 h, whereupon 18.8 g (0.100 mol) of dimethyldiselenide¹⁶⁵ in 50 ml of ether was added (-65°C). After stirring for 1 h, the reaction mixture was allowed to reach room temperature. Water was added and the organic layer was washed with 2 N HCl, water and dried. Evaporation and distillation yielded 7.5 g (51 %) of the title compound, b.p. $95-97^{\circ}\text{C}$. ^1H nmr (CCl_4): $\delta_{4\text{H}} = 6.83$ ppm (s, 1H); $\delta_{\text{SeCH}_3} = 2.28$ ppm (t, 3H). $J_{\text{Se-CH}_3} = 12$ Hz. ^{77}Se nmr (acetone- d_6): see 2.4. [Found: C 20.60; H 1.40; Cl 24.28; Se 53.80. Calc. for $\text{C}_5\text{H}_4\text{Cl}_2\text{Se}_2$ (292.91): C 20.50; H 1.38; Cl 24.21; Se 53.91.]

b) Lithium methylselenolate was prepared according to Ref. 166 in 100 ml of liquid ammonia from 0.28 g (0.040 mol) of lithium and 3.8 g (0.020 mol) of dimethyl diselenide. The solvent was evaporated and 100 ml of ether was added to the white residue. To this suspension, 3.26 g (0.0100 mol) of 2,5-dichloro-3-iodoselenophene (71) in 25 ml of ether was added. Samples were withdrawn, hydrolyzed and analyzed by vpc (column OV 17, 3 %, $80-200^{\circ}\text{C}$, $8^{\circ}/\text{min}$). It was evident upon mixing with authentic samples that the reaction was rather slow, and after 2.5 h about 30 % conversion to 73 had occurred. When the reaction was performed entirely in liquid ammonia, about the same result was achieved, except that some 2,5-dichloroselenophene was also formed.

Experimental part of Chapter 3.3.5

1,4-Cyclododecadione¹⁶⁸ (162) was prepared as described in Ref. 67. A solution of 100 g (0.549 mol) of cyclododecanone (EGA, m.p. $59-61^{\circ}\text{C}$) in 900 ml of petroleum ether (60-80) was irradiated with a 100 W medium pressure mercury lamp (Hanovia) for 3 days. The solvent was evaporated and the crude bicyclo-[8.2.0]dodecan-1-ol (100 g) was oxidized with "Jones solution" to give the title compound. The yield was 40.0 g (37 %) after crystallization from hexane, m.p. $77-79^{\circ}\text{C}$ (lit.¹⁶⁸ $78-80^{\circ}\text{C}$).

1,4-Cyclopentadecadione (163). A solution of 25.0 g (0.111 mol) of cyclopentadecanone (Fluka, m.p. $63-64^{\circ}\text{C}$) in 900 ml of hexane was irradiated until the carbonyl absorption in

the infrared had disappeared (48 h). This procedure was repeated 10 times, to give 250 g of a crude product which was believed to contain bicyclo[11.2.0]cyclopentadecan-1-ol. (When the solutions were more concentrated (>5 %) with respect to cyclopentadecanone the carbonyl absorption did not disappear even after irradiation for 100 h.) The crude product (250 g) was oxidized with Jones' reagent as above, which gave 216 g of a colourless oil which showed a strong carbonyl absorption in the infrared (1720 cm^{-1}), but no hydroxylic band. Combined vpc-mass spectrometry (column OV 1, 3 %, $150\text{--}300^\circ\text{C}$, $10^\circ/\text{min}$) showed mainly two components in the proportions 1:3, with $m/e = 138$ and 238. The most abundant compound was evidently the title compound (calc. for $\text{C}_{15}\text{H}_{26}\text{O}_2 = 238$). The crude product was used without purification.

[8](2,5)-Thiophenophane⁶⁶ (38) was prepared as described in Ref. 67 from 40.0 g (0.204 mol) of 1,4-cyclododecadione (162) in 1 l of ethanol (99.5 %), hydrogen sulphide and hydrogen chloride at 0°C ; yield 8.0 g (20 %) of 38, b.p._{1.0} $75\text{--}80^\circ\text{C}$ (lit.⁶⁶ b.p._{1.5} $80\text{--}81^\circ\text{C}$). The yield reported in Ref. 67 (80 %) could not be reproduced despite several attempts. (Large amounts of a nice-smelling yellow resin were formed.)

[11](2,5)-Thiophenophane (39).

a) A solution of 37.0 g (0.155 mol) of 1,4-cyclopentadecadione (163) in 1 l of ethanol (99.5 %) was cooled to 0°C and hydrogen sulphide and hydrogen chloride were bubbled through the solution for 8 h (cf. Ref. 67). The temperature was kept below $+5^\circ\text{C}$, and subsequently most of the solvent was evaporated. The residue was taken up in hexane, washed with water and dried. Evaporation of the solvent gave 30.4 g of a yellow oil which was dissolved in hexane and chromatographed on a silica gel column. Thus a fraction weighing 7.4 g was obtained, which gave 1.5 g (4.1%) of the title compound in the cold (-25°C). Recrystallization from acetonitrile (-25°C) afforded pure 39, m.p. $51\text{--}53^\circ\text{C}$. Nmr (CCl_4): $\delta_{\text{BH}} = 6.52\text{ ppm (s, 2H)}$; $\delta_{\text{-CH}_2\text{-}} = 2.6\text{--}2.9\text{ ppm (m, 4H)}$ and $0.6\text{--}1.8\text{ ppm (18H)}$. [Found: C 76.17; H 10.25; S 13.56. Calc. for $\text{C}_{15}\text{H}_{24}\text{S}$ (236.42): C 76.21; H 10.23; S 13.56.]

b) A mixture of 150 g (0.629 mol) of 163 and 100 g (0.450 mol) of P_2S_5 was heated at 80°C for 4 h under nitrogen (cf.

Ref. 66). The reaction mixture was cooled and extracted with hexane, whereupon the combined organic extracts were washed with 2 N aq. NaOH, water and dried. The solution was filtered through silica gel and the solvent was evaporated to give 55.2 g (37 %) of almost pure title compound. Crystallization from acetonitrile afforded 30.0 g (20 %) of 39 with the same properties as mentioned above.

Attempted synthesis of 3-bromo-[8](2,5)-thiophenophane (40).
Samples of 1.2 g (6.2 mmol) of [8](2,5)-thiophenophane (38) were treated as follows:

a) With bromine (1.0 g, 6.3 mmol) in 25 ml of acetic acid at room temperature for 30 min. After the usual work-up (hexane-extraction), 1.4 g of a crude product was obtained. Nmr (CCl_4) showed an AB quartet: $\delta = 6.83$ ppm (d) and $\delta = 6.62$ ppm (d). ($J = 3.4$ Hz) and several absorptions in the aliphatic region.

b) With NBS (1.1 g, 6.2 mmol) in 25 ml of acetic acid. A yellow crude product containing several components according to vpc (column OV 1, 3 %, 100-300°C, 15°/min) was obtained.

c) With bromine (1.0 g, 6.3 mmol) in 10 ml of pyridine. A yellow resin that did not give a reproducible gas chromatogram was obtained.

3-Bromo-[11](2,5)-thiophenophane (41). To a solution of 15.0 g (0.0634 mol) of [11](2,5)-thiophenophane (39) in 500 ml of acetic acid, 10.4 g (0.065 mol) of bromine in 50 ml of acetic acid was added dropwise at room temperature. The mixture was stirred for 2 h, neutralized with NaHCO_3 and extracted with ether. Drying and evaporation yielded 17.5 g of a crude product containing three components (2:2:5) according to vpc (column OV 1, 3 %, 200-300°C, 10°/min). Distillation of 15.0 g of the crude product gave 5.2 g (30 %) of the title compound, b.p. 5.10^{-3} 140-144°C, which crystallized. Recrystallization from DMF in the cold (-25°C) gave 4.3 g of pure 41, m.p. 45-46°C. Nmr (CDCl_3): $\delta_{4\text{H}} = 6.57$ ppm (s, 1H); $\delta_{-\text{CH}_2-} = 2.60-2.95$ ppm (m, 4H) and 0.60-1.85 ppm (m, 18H). [Found: C 56.6; H 7.39; S 10.3. Calc. for $\text{C}_{15}\text{H}_{23}\text{BrS}$ (315.32): C 57.14; H 7.35; S 10.17.]

Experimental part of Chapter 3.4

1,3-Hexadiyne was prepared according to Ref. 84c from 50.0 g (0.407 mol) of 1,4-dichloro-2-butyne, 28 g (1.2 mol) of sodium in 360 ml of liquid ammonia and 68 g (0.44 mol) of diethylsulphate; yield 15 g (47 %) of the title compound, b.p.⁵⁰⁻⁴⁰ 30-40°C (lit.^{84c} b.p.₁₂₀ 50°C, 59 %).

2,4-Heptadiyne¹⁷⁰⁻¹⁷² (109). To a solution of 14.0 g (0.179 mol) of 1,3-hexadiyne in 100 ml of ether, 130 ml (0.185 mol) of 1.42 M butyllithium in hexane was added at -50°C followed by 28.5 g (0.200 mol) of methyl iodide after 10 min. The reaction was followed by vpc (column OV 17, 3 %, 70-150°C, 10°/min) of hydrolyzed samples. Since no conversion had occurred after 1/2 h, 50 ml of dry HMPA was added. An exothermic reaction took place and the starting material was completely consumed 5 min after the addition of HMPA. The reaction mixture was poured into ice-water, extracted with ether and dried. The ethereal solution was filtered and 50 ml of decalin was added. The ether was distilled off at ordinary pressure, whereupon the pressure was lowered to 100 mm Hg. A fraction was collected between 60 and 70°C, and it was redistilled to give 9.2 g (56 %) of the title compound, b.p.⁷⁰⁻⁹⁰ 75-85°C (lit.¹⁷¹ b.p.₃₂ 59-60°C). Nmr (CCl₄): δ_{1H} = 1.90 ppm (t, 3H); δ_{6H} = 2.25 ppm (q with fine structure, 2H); δ_{7H} = 1.17 ppm (t, 3H). $J_{1H,6H}$ = 1.0 Hz; $J_{6H,7H}$ = 7.0 Hz.

ABBREVIATIONS

BuLi	Butyllithium
DDQ	2,3-Dichloro-5,6-dicyano-1,4-dibenzoquinone
DMA	Dimethylacetamide
DMF	Dimethyl formamide
DMS	Dimethyl sulphate
EtLi	Ethyllithium
HAc	Acetic acid
HMPA	Hexamethyl phosphorous triamide
NBS	N-Bromosuccinimide
NCS	N-Chlorosuccinimide
PTS	para-Toluenesulphonic acid
TBA	Tetrabutyl ammonium hydrogen sulphate
TTN	Thallium trinitrate trihydrate
ms	Mass spectrometry
vpc	Vapor phase chromatography
b	Broad
s	Singlet
d	Doublet
t	Triplet
q	Quartet

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